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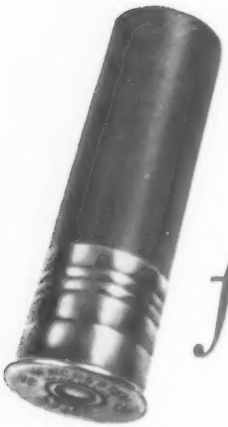

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1957

ORIGINAL ARTICLES

CLINICAL MANIFESTATIONS OF HYPOPOTASSEMIA*

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Patients with abnormally low concentrations of plasma potassium (hypopotassemia) may have numerous functional (Black[5], Bodansky[7], Danowski *et al.*[13], Darrow and Pratt[15], Elkinton and Danowski[16], Elliel, Pearson and Rawson[17], Elman *et al.*[19], Evans[21], Fourman[23], Frenkel, Groen and Willebrands[25], Hollender[28], Howard and Carey[30], Lans *et al.*[35], Martin *et al.*[41] Mudge[43], Patton *et al.*[45], and Randall *et al.*[47] and anatomic (Foye and Feichtmeir[24], Keye[34], McAllen[39], Perkins, Petersen and Riley[46], Rodriguez, Wolfe and Bergstrom[48], and Schwartz, Cohen and Wallace[51]) derangements. However, the majority of signs and symptoms attributed to hypopotassemia are nonspecific, being found in many severely ill persons without low potassium levels. Moreover, multiple disturbances of homeostasis nearly always complicate potassium deficiency and may obscure or modify its effects. Therefore, the association of a given clinical abnormality with hypopotassemia does not necessarily indicate that the abnormality is caused by hypopotassemia *per se*. The frequency of different signs and symptoms occurring in hypopotassemia has not been investigated systematically in relation to the

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plasma potassium level. Such an investigation forms the basis of this report. It was carried out on a fairly large patient material and includes a study of electrolytes other than potassium, as well as an examination of the hypopotassemic patients before and after potassium administration.

Material and Methods. Fifty adult patients with serum potassium levels below 3.5 mEq./L. were selected for the study from the morning records of the Clinical Chemistry Laboratory over a period of 7 months. Examination was performed in the evening, usually on a patient with the lowest morning serum potassium level, and consisted of: a) review of the history with attention to factors which are known to cause hypopotassemia; b) physical examination; c) dynamometer evaluation of hand strength; d) twelve-lead electrocardiogram; e) determination of venous plasma potassium, sodium, chloride, calcium and CO_2-combining power, as well as hematocrit and whole blood pH. Potassium chloride infusion was then begun, barring renal insufficiency or other possible clinical contraindications, according to the following formula: Potassium dose in mEq. = (5.0 − morning serum potassium level in mEq./L.) × (Wgt. in kg. × 0.2). In a few patients the calculated dose was somewhat exceeded.

Potassium was administered at a rate of 8 ml. per minute in a concentration of 60 mEq. per liter of 0.45% saline. In 5 patients for whom sodium chloride was contraindicated, potassium was given as a solution of 60 mEq. per liter of distilled water. The average dose of 34 mEq. (range: 21 to 60 mEq.) was given in an average time of 71 minutes (range: 45 to 120 minutes). The electrocardiogram was checked at intervals of 2 to 5 minutes during the infusion. Studies listed above (a–e) were repeated 15 minutes after completion of the infusion.

Since the intravenous dose generally was inadequate for correction of potassium deficiency, in each case repletion was attempted by means of energetic oral or parenteral therapy. Total or partial correction of deficiency was assumed to have occurred when plasma potassium stabilized at a normal concentration. However, because of deaths and ineffective therapy, presumable correction of deficiency was achieved in only 27 of the 50 patients. Those patients were then re-evaluated as described above.

Chemical methods were as follows: plasma sodium and potassium by internal standard flame photometry; calcium by oxalate precipitation (Clark and Collip[12]); chloride by the method of Volhard; whole blood pH with the model G Beckman pH meter.

TABLE 1.—MORTALITY

Service	No. of Admissions	Mortality: All Patients %	Mortality: Patients with Hypopotassemia %
Medical services including neurology	3834	23.9	54.6
Surgical services	2335	8.0	42.9
Gynecological service excluding maternity	1407	1.4	14.3
All services	7576	15.0	49.1

In addition, mortality rates were evaluated for all hospital patients who had had hypopotassemia at some time during the 7-month period of study.

Results. INCIDENCE OF HYPOPOTASSEMIA. During the period from October 1, 1954, to April 30, 1955, serum potassium concentration was determined in the Clinical Chemistry Laboratory of the Philadelphia General Hospital in 1497 adult males and 1289 adult female in-patients. Serum potassium concentrations below 3.5 mEq./L. were found in 273 men (18.3%) and in 284 women (22%).

MORTALITY OF PATIENTS WITH HYPOPOTASSEMIA. During the period of study, the mortality of patients with hypopotassemia greatly exceeded the total hospital fatality rate. As indicated in Table 1 this also was true for each of the individual services.

CHARACTERISTICS OF THE PATIENTS

STUDIED. The patients who were studied consisted of 20 males and 30 females, aged 18 to 85. The list of diseases in these patients (Table 2) was headed by hepatic cirrhosis (10 patients, 6 of whom were in hepatic coma).

potassium level. Group A consisted of 17 patients whose plasma potassium concentration was between 2.0 and 2.7 mEq./L., group B of 13 patients with levels from 2.71 to 2.98 mEq./L., and group C with levels from 3.0 to 3.49 mEq./L. The average and the ranges

TABLE 2.—CLINICAL DIAGNOSES IN FIFTY PATIENTS WITH HYPOPOTASSEMIA

Clinical Diagnosis	*No. of Patients*
Hepatic cirrhosis	10
Cerebrovascular accident	4
Intestinal obstruction	4
Azotemia	3
Carcinoma of rectosigmoid	2
Hypertensive encephalopathy	2
Postgastrectomy	2
Marginal peptic ulcer, functional pylorospasm, pancreatic fistula, carcinoma of stomach, peritonitis with pelvic inflammatory disease, postcholecystectomy, traumatic tear of liver, acute bacterial endocarditis, meningitis, septicemia, pemphigus, chronic malnutrition with pneumonia, metastatic carcinoma of breast, multiple myeloma with renal insufficiency, dissecting aortic aneurysm, myocardial infarction with shock, pulmonary tuberculosis with secondary amyloidosis, acute and chronic alcoholism, nephrotic syndrome, diabetic acidosis, cholelithiasis with pneumonia, pyoderma and silicosis, undiagnosed neurological disorder with malnutrition	1 each
Total	50

CAUSES OF HYPOPOTASSEMIA. In nearly every case there were several factors which could have been responsible for the hypopotassemia. There was an average of nearly three etiologic factors per case, and only one patient had but a single factor. These factors occurred with the following frequency: inadequate diet in 84%; infusions of potassium-free solutions in 52%; vomiting in 46%; suction and gastrointestinal fistulas in 24%; diarrhea in 24%; renal disease in 20%; administration of steroids in 10%; prolonged treatment with diuretics in 8% and insulin administration in 2%.

PLASMA ELECTROLYTES AND VENOUS PH. The patients were divided into three groups on the basis of plasma

of the concentrations of sodium, chloride, calcium and the pH in the three groups are indicated in Tables 3 to 6. It can be seen that the patients with the lowest plasma potassium level also had the lowest concentrations of chloride and calcium and were more often alkalotic. Plasma sodium concentration was not appreciably different in the three groups.

CLINICAL SYMPTOMS. 1. *Anorexia, Nausea and Vomiting.* Because of anorexia, nausea or vomiting 42 (84%) of the patients required parenteral potassium administration when repletion was attempted. Table 7 indicates the oral food intake at the time of evaluation and demonstrates the poor correlation between the degree of anorexia

and of hypopotassemia. Two patients of group A had normal appetites, with plasma potassium levels of 2.64 and 2.67 mEq./L. In 2 patients, improved appetite occurred due to disappearance of nausea immediately after intravenous potassium administration. After repletion, improvement of appetite or disappearance of nausea occurred in 8 further subjects.

2. *Abdominal Distention and Decreased Bowel Sounds.* Measurement of abdominal circumference before and after potassium administration was found to be inaccurate and was abandoned early in the study. Bowel sound intensity was graded zero to four plus; two and three plus were considered normal. Decreased or absent bowel sounds were found in 25 patients, in 6 of whom increased peristaltic activity was evident 15 minutes after potassium infusion. There was no correlation between the degree of impairment of intestinal motility and the degree of hypopotassemia. In some cases the distention was severe enough to warrant the designation of paralytic ileus. The following is an illustrative case:

CASE NUMBER 4. J.B., a 61-year-old male was admitted with a history of anorexia and vomiting. He was lethargic and disoriented

TABLE 3.—PLASMA SODIUM CONCENTRATION IN HYPOPOTASSEMIA

Group	Range of plasma K in mEq./L.	No. of Cases	Range of plasma Na in mEq./L.	Average plasma Na in mEq./L.	Plasma Na > 150 mEq./L. No. of cases	Plasma Na 130–149 mEq./L. No. of cases	Plasma Na < 129 mEq./L. No. of cases
A	2.0 —2.7	17	120—168	136	2	10	5
B	2.71—2.98	13	123—170	137.1	2	7	4
C	3.0 —3.49	20	126—171	141.6	6	10	4

TABLE 4.—PLASMA CHLORIDE CONCENTRATION IN HYPOPOTASSEMIA

Group	Range of Plasma K in mEq./L.	No. of Cases	Range of plasma Cl in mEq./L.	Average plasma Cl in mEq./L.	Plasma Cl > 90 mEq./L. No. of cases	Plasma Cl < 90 mEq./L. No. of cases
A	2.0 —2.7	16	55—114	82.7	7	9
B	2.71—2.98	12	77—148	92.3	4	8
C	3.0 —3.49	19	72—129	95.2	13	6

TABLE 5.—PLASMA CALCIUM CONCENTRATION IN HYPOPOTASSEMIA

Group	Range of plasma K in mEq./L.	No. of Cases	Range of plasma Ca in mEq./L.	Average plasma Ca in mEq./L.	Plasma Ca > 4.25 mEq./L. No. of cases	Plasma Ca < 4.25 mEq./L. No. of cases
A	2.0 —2.7	16	3.05—5.35	4.05	6	10
B	2.71—2.98	11	3.55—5.30	4.29	7	4
C	3.0 —3.49	17	3.70—6.60	4.54	14	3

TABLE 6.—pH OF THE VENOUS BLOOD IN HYPOPOTASSEMIA

	Range of plasma K	No. of cases	Range of blood pH	Average blood pH	pH > 7.45 No. of cases	pH 7.34–7.45 No. of cases	pH < 7.34 No. of cases
A	2.0 —2.7	15	7.30—7.60	7.46	7	6	2
B	2.71—2.98	8	7.29—7.61	7.46	3	3	2
C	3.0 —3.49	15	7.28—7.48	7.39	4	10	1

TABLE 7.—ORAL FOOD INTAKE OF PATIENTS WITH HYPOPOTASSEMIA AT THE TIME OF EXAMINATION

			Satisfactory		*Nonsatisfactory*							
			Normal appetite		*Nausea, vomiting, anorexia*		*Nothing "p.o."*		*Nausea and vomiting*		*None*	
Group	*Range of plasma K mEq./L.*	*No. of patients*	*No. of patients*		*No. of patients*		*No. of patients*		*No. of patients*		*Coma, stupor*	
											No. of patients	
A	2.0 — 2.7	17	2		2		2		2		9	
B	2.71 — 2.98	13	2		3		1		2		5	
C	3.0 — 3.49	20	4		4		4		4		4	
	Total	50	8		9		7		8		18	

and unable to take food by mouth. Dehydration was marked. Blood pressure was 190/100. Respirations were shallow, 24 per minute. The abdomen was markedly distended and a flat film of the abdomen revealed marked small and large bowel distention suggesting paralytic ileus. The electrocardiogram was typical of hypopotassemia. The plasma electrolytes were as follows: potassium, 2.56; sodium, 143; chloride, 102; and CO_2 20 mEq./L. The hematocrit was 28% and the pH 7.41. After administration of 54 mEq. potassium within 80 minutes, the plasma potassium was 2.97 mEq./L. and the blood pH 7.38. During the infusion flatus was passed and the abdominal girth decreased by 1.5 cm. Following further administration of potassium the abdominal distention disappeared completely.

COMMENT. Paralytic ileus was relieved promptly after potassium infusion.

In 8 patients there was increased intestinal motility immediately after intravenous potassium administration. Distention was relieved or the bowel sounds became more active after several days of potassium administration in 12 other patients. Sometimes the effect of intravenous potassium on peristalsis was striking; certain patients manifested flatulence and one developed painful abdominal cramps during the infusion.

3. *Type and Rate of Respiration.* In no case did we see stridor (Black, Davies and Emery[6]), respiratory paralysis, "gasping" or "fish-mouth" breathing (Martin and Wertman[42]). Patients with normal and abnormal respiratory patterns were fairly evenly distributed among the three groups. After potassium infusion, the respirations became slower and deeper in 6 patients, and more rapid in 5 patients.

4. *Blood Pressure.* After potassium administration there was a slight increase in average systolic pressure in groups A (from 123 to 128 mm. Hg) and B (from 114 to 121 mm. Hg). However, the changes in average value are too small to be of significance and

in each group a rise in blood pressure was about as common as a fall during infusion. The largest individual increase in the systolic pressure was 30 mm., in the diastolic pressure was 23 mm. and in the pulse pressure 45 mm. The largest individual decrease in the systolic pressure was 30 mm., in the diastolic pressure 10 mm. and in the pulse pressure 30 mm. In 19 patients studied after repletion of potassium deficiency, the average systolic pressure was about 3 mm. and the average pulse pressure about 4 mm. lower than at the time of hypopotassemia.

5. *Other Cardiovascular Manifestations.* Eighteen patients had a heart murmur. However, in only 3 did the intensity decrease after potassium administration. In 2 patients, an apical systolic murmur became softer and in one subject a murmur and evidence of cardiac dilatation disappeared entirely after correction of potassium depletion. The following case is of interest:

CASE NUMBER 5. C.B., a 55-year-old female alcoholic was admitted because of vomiting, semi-coma and marked dehydration. The blood pressure was 145/80 and the heart rate 80 per minute. The apex beat was diffuse, heaving and outside the midclavicular line. A grade IV, rough apical murmur occupied all of the systole. The electrocardiogram was typical of hypopotassemia. The plasma electrolyte values were as follows: potassium, 2.36; sodium, 123; calcium, 4.4; chlorides, 63 mEq./L. The pH was 7.60. Blood urea nitrogen was more than 180 mg. per 100 ml. Following administration of 38 mEq. of potassium during an 80-minute period, the potassium concentration rose to 3.5 mEq./L. and the blood pH was 7.59. She was more alert, and bowel sounds more active. Ten hours later, after an additional 40 mEq. of potassium intravenously, there was a decrease in the intensity of the apical heave and murmur. After 2 days of therapy, the plasma potassium was 4.2 mEq./L. and the blood urea nitrogen was 80 mg. per 100 ml. The apex beat was found to be within the midclavicular line and the murmur could no longer be heard. At this time the patient started taking food and KCl by mouth, and 2 days later her plasma potassium was 5.1, sodium 124, chloride 95 mEq./L. The pH was 7.40 and the blood urea nitrogen 19 mg. per 100 ml. The patient was well hydrated and alert. The electrocardiogram was normal and the chest film revealed normal cardiac silhouette.

COMMENT. Cardiac dilatation and a loud murmur disappeared following potassium therapy and hydration. Hypopotassemia may have contributed to the severe azotemia by depression of glomerular filtration rate (Burnett, Burrows and Commons[9], Kennedy, Winkley and Dunning[33], MacGregor and Fitz[40], and [57]).

6. *Muscular Strength.* Only half of the patients were able to cooperate in squeezing the dynamometer. A pressure of 40 pounds produced by squeezing with one hand was considered normal for a male; for a female, 30 pounds was judged normal. Muscle weakness was present in 21 out of 23 patients subjected to the test, but there was no correlation between the degree of weakness and severity of hypopotassemia. After potassium infusion, a significant increase in strength, that is, more than 10 pounds, occurred in only 4 of the 23 patients. Two were in group A, one in B and one in C.

7. *Deep Tendon Reflexes and Neuromuscular Irritability.* In 5 patients, all of the tested deep tendon reflexes (knee, ankle, biceps and triceps jerks and radial periosteal reflexes) were absent; they were in group A. In further 12 patients, the reflexes were markedly decreased; 4 were in group A, 7 in group B and 1 in group C. In 18 patients the reflexes were normal or hyperactive; 3 were in group A, 2 in group B and 13 in group C. Thus, there appeared to be some correlation between the degree of hyporeflexia and hypopotassemia. However, intravenous administration of potassium was followed by increased activity of the re-

flexes in only 4 cases. In the 5 subjects with absence of all deep tendon reflexes, intravenous potassium chloride failed to produce a change.

Chvostek's sign was positive in only 2 cases and muscular twitchings were present in another. The potassium level was below 2.7 mEq./L. in each, 2 had hypocalcemia (calcium 3.44 and 3.85 mEq./L.) and one had alkalosis (pH 7.58) with normal calcium. However, there were numerous patients with equal degrees of hypocalcemia or alkalosis who had no Chvostek's sign or twitching. Tetany did not occur in a single case during or after potassium administration.

8. *Mental Status.* Seven patients were in coma, 15 were semicomatose, confused and delirious, 17 were lethargic, listless or stuporous, 2 showed signs of increased irritability and only 9 patients had no abnormalities of the mental status. All of the encountered abnormalities of the mental status occurred in all three groups. However, severe abnormalities were most common in group A, while normal mental status was most common in group C. Intravenous administration of potassium was accompanied by rapid improvement of mental status in 11 patients.

TABLE 8

Number of Patients Showing Change	*Changes Observed Following I.V.KCl*
11	Increase of systolic blood pressure more than 10 mm.
11	Improved mental status
9	Increased peristaltic activity
9	Slowing and deepening of respiration
6	Drop of systolic blood pressure more than 10 mm.
4	Increased rate of respiration
4	Increased muscle strength
4	Increased deep tendon reflexes
2	Disappearance of nausea

CLINICAL EFFECTS OF INTRAVENOUS POTASSIUM ADMINISTRATION. A change in physical or mental status following potassium infusion was observed in 26 out of 42 patients (Table 8).

In 4 patients, three effects were noted, 3 patients had four changes, and in one patient, five effects were seen.

The following case is illustrative of several changes after intravenous KCl administration:

CASE NUMBER 43. R.S. was a 38-year-old man admitted in hepatic coma and hemorrhagic shock due to bleeding varices and Laennec's cirrhosis. Before our evaluation he had had several liters of intravenous saline and glucose. The plasma potassium level was 2.83, sodium 157, calcium 4.1 chloride 93 mEq./L., pH 7.55, hematocrit 33%. He was lethargic and disorientated. The blood pressure was 98/47. The bowel sounds were hypoactive, and deep tendon reflexes were absent. The electrocardiogram was typical of hypopotassemia. After administration of 30 mEq. of potassium in one hour, the plasma potassium was 3.21 mEq. and the pH was 7.52. The blood pressure rose to 120/70, the respirations increased to 24 per minute and became deeper. The patient became more alert, the bowel sounds were more active and several tendon reflexes could be obtained. After 9 days of dietary and supplemental potassium the blood pH remained high (7.48) and the potassium low (3.76 mEq.) but the clinical status was good.

COMMENT. A relatively small potassium infusion promptly produced several types of improvement in the clinical state. However, hypopotassemia and alkalosis were slow to recede. Difficulty with potassium repletion and repair of alkalosis has been noted previously in patients with liver cell failure (Amatuzio *et al.*[2]).

The amount of increase in plasma potassium concentration and the post-infusion potassium level were not correlated with the presence or absence of potassium effects.

EFFECT OF POTASSIUM INFUSION ON PLASMA POTASSIUM VALUES AND THAT OF OTHER ELECTROLYTES. The amount of

TABLE 9.—CHANGES IN PLASMA POTASSIUM CONCENTRATION AFTER INTRAVENOUS KCl ADMINISTRATION

Group	Range of plasma K mEq./L.	No. of cases	Increase in plasma K in mEq./L.		Amount of administered K in mEq./L.	
			Range	Average	Range	Average
A	2.0 —2.7	11	0.24—1.25	0.84	30—60	45
B	2.71—2.98	11	0.15—2.05	0.74	24—45	30
C	3.0 —3.49	14	0.12—1.06	0.53	21—38	28

TABLE 10.—CHANGE IN PLASMA SODIUM, CALCIUM, CHLORIDE, CO_2 AND BLOOD pH AFTER INTRAVENOUS POTASSIUM ADMINISTRATION

	No. of Cases	Unchanged No. of cases	Increased No. of cases	Decreased No. of cases	Range of change in mEq./L.	Average change in mEq./L.
Plasma Na	37	4	12	21	—19 to +22	—1.75
Plasma Ca	26	3	10	13	— .2 to + .9	+ .06
Plasma Cl	29	3	11	15	—28 to +15	—0.38
CO_2-comb. power	21	4	4	13	— 6.2 to + 1.1	—2.2
Ven.blood pH*	24	3	6	14	— .13 to + .14	— .022

* units

increase in potassium concentration appears to be well correlated with the degree of initial hypopotassemia and the dose of administered potassium (Table 9). In several patients, blood samples immediately following and 15 minutes after KCl administration were compared, and in each instance a significant decrease in potassium concentration was found.

Changes in concentration of other electrolytes and of blood pH are presented in Table 10. There was no consistent change in chlorides or calcium concentration after potassium administration. Decrease in plasma sodium was more frequent than an increase; it should be noted that the infusion was hypotonic with respect to sodium. Fall of CO_2 concentration and of pH was significantly more frequent than a rise. The direction of the chemical changes were about the same in all three groups of patients.

CLINICAL EXAMINATION AFTER PRESUMABLE CORRECTION OF POTASSIUM DEFICIENCY. Normal and stable plasma levels were obtained in 27 patients following parenteral and oral potassium administration. Most commonly, 3 to 6 days were required. In 16 subjects, all clinical signs and symptoms originally attributed to hypopotassemia disappeared after stabilization of normal potassium levels. Thus, increased alertness was observed in 13 patients, increased muscle strength in 9, and elevation of blood pressure in 7 patients.

In 11 patients, one of the following signs or symptoms originally attributed to hypopotassemia persisted after presumable correction of potassium deficiency: absent tendon reflexes in 5, muscular weakness in 3, hypoactive bowel sounds in 2, mental dullness or apathy in 2, disorientation, one, and coma in one.

Discussion. Hypopotassemia was found in about one-fifth of Philadelphia General Hospital in-patients in whom this measurement was made. A similar incidence has been reported from other hospitals (Martin *et al.*[41], and Patton *et al.*[45]). We have recorded separately the frequency of hypopotassemia in men and women because females outnumber the males in the group studied. This appeared to be of possible significance in connection with the lower value for exchangeable potassium in women as compared with men (Aikawa, Harrell and Eisenberg[1]). The higher incidence of hypopotassemia in women of our material was of definite statistical significance (p equals less than 0.01).

The mortality rate of patients who had hypopotassemia was much higher than the general hospital fatality. This implies that hypopotassemia is a frequent accompaniment of life-threatening illness. The high mortality of postoperative patients with hypopotassemia has been stressed by Patton *et al.*[45].

The list of diseases diagnosed in our patients is a long one. The fact that 20% of the subjects had liver cell failure emphasizes the very frequent association of the latter with hypopotassemia (Artman and Wise[4]).

Inadequate potassium intake was of etiologic importance in nearly every case, though in most patients several factors were involved. The etiology of hypopotassemia in 150 patients reported by Martin *et al.*[41] was similar.

The correlation between hypopotassemia and hypochloremia was not surprising, nor was the common occurrence of alkalosis. However, the incidence of hypocalcemia was surprisingly high and we are unable to determine whether or not the correlation between the severity of hypopotassemia and hypocalcemia was fortuitous.

Although hypocalcemia was common, clinical manifestations were rare and in no case did tetany occur during

potassium administration, as may happen when potassium is given in the presence of hypocalcemia (Engel and Martin[20]).

Clinical manifestations of hypopotassemia will be discussed in relation to: 1) frequency of occurrence, 2) correlation with the severity of hypopotassemia, and 3) specificity.

1) Frequency of occurrence. The frequency of the various clinical manifestations is presented in Table 11. Our results are fairly similar to the results of Elliel *et al.* obtained in 30 postoperative patients with potassium deficiency[17]. Although muscular paralysis has been reported in 6 out of 309 hypopotassemic surgical patients (Lans, Stein and Meyer[36]), it did not occur in our experience nor in that of Elliel *et al.*[17]. The lowest plasma potassium level in our material was 2.0 mEq./L. and it has been suggested that muscular paralysis appears when the concentration is below 1.9 mEq./L. (Hollender[28]). However, poor correlation of extracellular potassium levels with muscle paralysis is well known in familial periodic paralysis (Danowski and Tarail[14]) and in other conditions. Thus, paralysis has been described in patients with potassium levels of 2.85 mEq./L. (Lubran and McAllen[38]), 2.5 mEq./L. (Holler[29], and Jackson and Oakley[31]), and 1.56 mEq./L. (Stephens[54]), while a patient with a concentration of 0.98 mEq./L. was reported to demonstrate merely weakness (Nelson, Friesen and Kremen[44]), and one patient with a value of 0.25 mEq./L. (Broch[8]) had no signs or symptoms of hypopotassemia whatsoever.

Cardiovascular abnormalities which could be ascribed to hypopotassemia apparently are not frequently detectable during physical examination. An exception to this is the appearance of arrhythmias which will be discussed together with the electrocardiographic findings (Surawicz *et al.*[56]). Manifest cardiac dilatation and loud murmurs which can be attributed to hypopotassemia appear infrequently. We have not found any consistent changes in systolic or pulse pressure in hypopotassemia, and we have not observed congestive heart failure which could be attributed to this electrolyte disturbance. A single observation of a high systolic and pulse pressure led Frenkel *et al.*[25] to conclude that hypopotassemia may be associated with high output cardiac failure. More frequently, however, hypopotassemia is incriminated as a cause of hypotension (Hollender[28], Lans, Stein and Meyer[36], MacGregor and Fitz[40], and Martin *et al.*[41]).

2) Correlation of severity of symptoms with the level of plasma potassium. A rough correlation between impairment of intestinal peristalsis and degree of hypopotassemia was reported by Schlesinger *et al.*[50]. Otherwise, the literature does not indicate a correlation between the severity of hypopotassemic symptoms and the extracellular potassium concentration. In our material, the correlation was poor with one exception, namely the activity of the deep tendon reflexes (Table 11). Thus, absence or significant hypoactivity of the deep tendon reflexes in hypopotassemic patients before treatment was nearly always associated with a plasma potassium level below 3.0 mEq./L., while nearly all patients with a level above 3.0 mEq./L. had normal or only slightly hypoactive reflexes. It must be stated that this correlation did not become apparent until the study was completed, and it may be fortuitous since almost all patients with absent or hypoactive reflexes were severely ill.

One would expect that muscular weakness would correlate as well as deep tendon reflexes with the extent

TABLE II.—INCIDENCE, CORRELATION WITH PLASMA POTASSIUM CONCENTRATION AND SPECIFICITY OF COMMON CLINICAL MANIFESTATIONS OF HYPOPOTASSEMIA

Clinical Manifestation	*Incidence of occur. in %*	*Correlation with plasma K conc.*	*Rapid changes after I.V. KCl administration*			*Changes after presumable correction of K deficiency*		
			No. of observ.	*Improved*		*No. of observ.*	*Improved*	
				No. of patients	*%*		*No. of patients*	*%*
Anorexia caused by nausea or vomiting	34	poor	17	2	12	7	5	72
Abdominal distention and hypoactive bowel sounds	52	poor	18	6	33	10	8	80
Abnormal resp. rate or pattern	64	poor	32	11	34	15	6	40
Hypoactive or absent deep tendon reflexes	64	fair	32	4	12	16	5	31
Impaired mental function	82	poor	37	11	29	17	13	78
Muscular weakness	91	poor	23	4	17	13	4	30

of hypopotassemia. However, our method of determining muscle strength was crude, required cooperation of the patient and therefore excluded the most severely ill patients. This may account for the poor correlation between muscular strength and severity of hypopotassemia observed in our series. Abnormal electromyograms have been recorded (Jackson and Oakley[31], Jantz[32], and Streeten and Vaughn Williams[55]), but to our knowledge no electromyographic study on a large group of patients with hypopotassemia has been carried out.

3) Specificity. Specificity of the clinical manifestations of hypopotassemia is difficult to evaluate. Because of alteration of other body electrolytes following potassium administration and various associated abnormalities in the clinical state, disappearance of certain signs or symptoms following potassium therapy is not definite evidence that they were due to hypopotassemia. In addition, some of the changes observed after infusion might be attributed to the effects of water, chloride or sodium received along with potassium. However, like other observers (Ariel[3], Callaway and Roemmich[10], Chassin and Slattery[11], Elliel *et al.*[17], Elman *et al.*[19], Frenkel *et al.*[25], Gazes *et al.*[26], Grieve[27], Lans *et al.*[35,36], Logan[37], Martin and Wertman[42], Sayers *et al.*[49], Wilson and Sink[58], and Winter *et al.*[59]) we have seen rapid improvement of mental status, slowing and deepening of respiration, increase in intestinal motility, disappearance of nausea, increase in muscle strength and increased activity of deep tendon reflexes after potassium infusion (Table 11).

Improvement of muscular strength and of neuromuscular defects following potassium administration has been found to be slow (Howard and Carey[30], and Sherry *et al.*[53]). Our finding that rapid improvement of mental function and intestinal motility was more common than rapid improvement of muscle strength and reflex activity is in accord with observations on the speed of uptake and exchange of potassium in various organs (Black, Davies and Emery[6], and Fenn *et al.*[22]).

After potassium deficiency presumably had been corrected, nausea and vomiting, mental depression and abdominal distention seldom persisted, while more than half the cases still showed an abnormal respiratory pattern, muscular weakness and decreased activity of deep tendon reflexes. Whether these findings mean that the neuromuscular symptoms are not very specific for hypopotassemia or that they are specific but require a longer time for improvement, cannot be answered on the basis of this study.

Summary. During a 7-month study, 557 cases of hypopotassemia were encountered in 2786 potassium determinations. The incidence among females was significantly higher than among males. The mortality of hypopotassemic patients was strikingly higher than the over-all hospital fatality rate.

Fifty hypopotassemic patients were selected for detailed evaluation. Several etiologic factors which could have been responsible for hypopotassemia were present in nearly every case. Hypochloremic alkalosis with hypocalcemia commonly accompanied potassium deficit. Patients with the lowest plasma potassium levels had also lowest plasma calcium and chloride levels and were more alkalotic.

Clinical abnormalities were of the type often encountered in seriously ill patients with or without hypopotassemia. Of all clinical abnormalities, only decrease of the activity of the deep tendon reflexes showed some correlation with decrease in plasma potassium level. Rapid infusion of potassium was used as a method of suggesting which of the signs and symptoms found

on initial examination might have been due to potassium deficiency. The most significant changes accompanying infusion were improved mental status and increased peristaltic activity. Further changes observed after several days of potassium repletion were difficult to evaluate, for many other therapeutic procedures also had been carried out. The nonspecific nature of the clinical manifestations of hypopotassemia in this seriously ill, mentally beclouded group of patients emphasizes the importance of electrocardiographic and other laboratory aids in the diagnosis of this disorder.

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(Interlingua on page 634)

SUMMARIO IN INTERLINGUA

(See page 617 for original article)

Meningitis a Listeria: Un Reporto de Octo Casos

Octo casos de meningitis a *Listeria* esseva admittite intra 4 annos al Section de Morbos Communicabile del Hospital del Contato de Los Angeles. Quatro del patientes moriva, e quatro se restabliva completemente. Omnes recipeva penicillina e sulfas, e omnes, con un exception, recipeva chloramphenicol como therapia initial. Cinque del 8 organismos esseva resistente a chloramphenicol. Un esseva sensibile solmente a penicillina. E un esseva resistente a omne le antibioticos testate.

Le bacteriologia de *L. monocytogenes* es passate in revista, e le tests laboratorial necessari pro le identification es sublineate.

Le sequente conclusiones esseva formulate. Grande attention debe esser prestate a que *Le monocytogenes* non es identificate erroneemente como diphtheroide o como un streptococco beta. Omne diphtheroides isolate ab fluidos spinal o ab culturas de sanguine deberea esser testate pro motilitate in un medio semisolide incubate a un temperatura normal de interior. Si le organismos es motil, su virulentia debe esser testate in muses e conilios, e un identification serologic debe esser interprendite.

L. monocytogenes varia grandemente in su sensibilitate a differente antibioticos. Tests de sensibilitate *in vitro* es de grande valor como guida in le selection del therapia pro le individuo ab qui le organismo esseva obtenite.

LISTERIA MENINGITIS, A REPORT OF EIGHT CASES

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The increasing number of cases of listeria meningitis reported in the literature in the past 5 years indicates that infection in man with *Listeria monocytogenes* is not so rare as was formerly believed. When human infection occurs it has a predilection for the central nervous system, causing meningitis, often rapidly fatal. Prior to 1952, only 20 cases of listeria meningitis were reported in the literature (Line and Cherry[4]). Since 1952 eleven additional cases of meningitis have been reported in the United States (Binder *et al.*[1], Line and Appleton[3], Line and Cherry[4], Mathieu *et al.*[5], Norman[6], Schulze, Wahle and White[7], Selinger and Becker[8], and Williams and Hornung[9]), and one case of subacute bacterial endocarditis (Hoeprich and Chernoff[2]). Several authors (Mathieu *et al.*[5], Norman[6], and Williams and Hornung[9]) emphasize the fact that due to its striking morphological resemblance to diphtheroids, and the colonial similarity on blood agar to beta streptococci, cultures of the organism may be discarded as contaminants or wrongly identified as beta streptococci. The obvious conclusion is that perhaps human listeriosis is more common than has been believed.

The isolation of *L. monocytogenes* from 8 cases of meningitis admitted to the Communicable Disease Unit of the Los Angeles County Hospital within a period of 4 years proves this assumption correct. All 8 patients presented a picture typical of purulent meningitis. The details of bacteriological and clinical interest are summarized in Table 1. In 6 of the 8 cases the spinal fluids had a predominance of polymorphonuclear cells. Before entering the hospital, the first case had been treated with penicillin and chlortetracycline and the initial spinal fluid had only 200 white blood cells, the majority of which were mononuclear. The spinal fluid in the eighth case was grossly bloody so an accurate determination of the leukocytes could not be obtained. *L. monocytogenes* was cultured from 8 spinal fluids, although the organism was found on direct smear in only 5 of the specimens. A blood culture was positive in the fourth case. Diphtheroid organisms grew in the blood cultures of 2 other patients: in one the organism was not tested for motility; in the other the diphtheroid was nonmotile and, therefore, it was assumed to be a contaminant.

Sensitivity tests on the organisms recovered from these patients were done by the disc method. Results are shown in Table 1. The sensitivities varied, but organisms from survivors were responsive *in vitro* to a larger number of antibiotics than those from the patients who died. It is noteworthy that 5 of the 8 organisms were resistant to chloramphenicol. All patients except one received chloramphenicol as part of the initial therapy.

TABLE 1.—RESULTS OF SENSITIVITY TESTS

Case No.	Age and Sex	Stay in Hospital	Admission Spinal			Bld. Cul.	Drugs Used in Therapy								Antibiotic Sensitivity						
			WBC	% PMN	Culture		P	St	Ca	Ct	O	T	E	Sulfa	P	St	Ca	Ct	O	T	E
1.	2-year Male	11–24–52 to 12–22–52	200	28	+	—	+	+			+			+	S	S	R	S	S	ND	ND
2.°	11-day Male	1–3–53 to 1–4–53	3000	60	+	—	+		+					+	S	R	R	R	R	ND	ND
3°	49-year Female	8–21–53 to 8–22–53	2800	85	+	—†	+		+					+	S	S	R	S	S	ND	S
4.°	75-year Male	9–30–53 to 10–2–53	2200	95	+	+	+		+		+			+	R	S	R	S	S	ND	R
5.	62-year Female	4–30–55 to 6–3–55	2000	90	+	—‡	+		+		+			+	S	S	S	S	S	S	S
6.	62-year Male	8–26–55 to 9–14–55	1300	90	+	—	+		+					+	S	S	S	S	S	S	S
7.	44-year Male	9–27–56 to 10–26–56	1000	92	+	—	+		+			+		+	S	S	S	S	S	S	S
8.°	14-day Female	11–26–56 to 11–29–56	Bloody		+	—	+	+	+		+			+	R	R	R	R	R	R	R

°Fatality
†Diphtheroid, nonmotile
‡Diphtheroid, motility not tested

P = Penicillin
St = Streptomycin
Ca = Chloramphenicol
Ct = Chlortetracycline
O = Oxytetracycline
T = Tetracycline
E = Erythromycin
S = Sensitive
R = Resistant
ND = Not done

The antimicrobial drugs used in these cases are shown in Table 1. The first patient, a 2-year-old child, did not respond well to initial medication and, therefore, received several antibiotics. The tuberculin skin test was positive and chest roentgenogram revealed a calcified lesion in the base of the right lung consistent with healed tuberculosis. Since his initial spinal fluid contained only 200 leukocytes per c.mm. with 72% lymphocytes, there was skepticism as to whether *L. monocytogenes* was causing the meningitis. Therefore, streptomycin was used in place of oxytetracycline. Extensive search for acid-fast bacilli in his spinal fluid was negative. By this time sensitivity tests showed the organism to be very sensitive *in vitro* to oxytetracycline and, therefore, treatment was reversed and this antibiotic was reinstated, and the patient became afebrile 8 days after entry.

The 11-day-old male and the 49-year-old female expired within 24 hours after admittance. The fourth case also died. When the organism from his spinal fluid was tentatively identified as *L. monocytogenes*, treatment was changed and oxytetracycline was substituted for chloramphenicol. This was done because of the results of the sensitivity tests on the organisms from the first and third cases. He did not respond and died within 72 hours after entry. The organisms from these fatalities were all resistant to chloramphenicol, which constituted part of the original therapy.

The fifth patient's initial response to therapy was good. However, her temperature did not fall below 100° for 12 days. Again oxytetracycline was substituted for all previous medications and the patient became afebrile 5 days later.

The sixth patient responded rapidly to therapy which consisted of penicillin, chloramphenicol, and equal parts of sulfadiazine and sulfamerazine in combination. The patient was afebrile 4 days after treatment was initiated.

The seventh case was treated initially with penicillin, chloramphenicol, sulfadiazine and sulfamerazine. Tetracycline was added to this routine 48 hours after admittance when the organism cultured from his spinal fluid was identified as *L. monocytogenes* but before *in vitro* sensitivities were completed. Treatment was discontinued after 18 days and recovery was complete and uneventful.

The last patient, a 14-day-old baby, had had an uncomplicated delivery and did well until 2 days before admittance to this hospital. The day it was admitted the child had anorexia, fever and diarrhea. Physical examination showed bulging fontanelles and a left facial weakness. The initial spinal fluid was grossly bloody. No fluid was obtained from right and left subdural taps. A cisternal tap produced 4 ml. of thick, blood-tinged fluid. Initial treatment consisted of penicillin, chloramphenicol, sulfadiazine and sulfamerazine. The baby had intermittent convulsions throughout its whole hospital stay, and its course was progressively downhill. By the second day the organism cultured from the spinal fluid was tentatively identified as *L. monocytogenes*. Since the child was not improving, the therapy was revised and streptomycin and oxytetracycline were substituted for chloramphenicol, but the child expired on the third hospital day. *In vitro* sensitivity tests read postmortem showed the organism to be resistant to all antibiotics.

It is of interest that pharyngitis existed in the first, fifth and sixth cases. An injection of the right eardrum in the first patient was noted and in the second case both tympanic membranes were dull, and the landmarks not

visible. The nasal membrane and eardrums of the seventh case were injected. This indicates that the primary focus of infection probably was the upper respiratory tract, although all cultures of the nasopharynx were negative for *L. monocytogenes*. Furthermore, the patient with a positive blood culture suggests that listeria meningitis is produced by hematogenous spread from the upper respiratory tract.

In patient No. 2 a papular rash was seen over the chest. This child died and on necropsy a blood clot was found at the base of the brain. Patient No. 4 had a generalized petechial rash. At necropsy this patient was shown to have a subdural hemorrhage as well as diffuse pulmonary hemorrhages and petechial hemorrhages of the colon. The liver was hemorrhagic and necrotic. Permission for necropsy on the third, fourth and eighth cases was not obtained.

BACTERIOLOGICAL STUDIES. *L. monocytogenes* is an aerobic, nonsporeforming, motile, Gram-positive bacillus. The length of the majority of organisms is 1 to 2 mu. An occasional rod is about 5 mu. in length and this gives a clue to the identity of the organism. Occasionally bacilli from cultures may occur in chains, although they usually tend to palisade and, therefore, bear a close morphological resemblance to diphtheroids. On Gram stains of the sediment from spinal fluids the organisms are often intracellular and may appear somewhat granular, thus resembling streptococci. The organism is sluggishly motile when grown at room temperature. If broth cultures are incubated at 37° C. the motility is usually lost after 6 to 8 hours. Therefore motility is best demonstrated by growth in a semisolid medium incubated at room temperature. The organism grows well on all types of media, colonies usually being well developed after 24-hours' incubation, but the organism from the eighth case grew more slowly and colonies were not apparent until after 48-hours' incubation at 37° C. *L. monocytogenes* is relatively inactive biochemically but produces acid regularly in glucose, rhamnose and salicin, and variably and more slowly in lactose, sucrose and maltose. Colonies on blood agar from primary isolates are smooth, translucent and about 1 mm. in diameter. Most strains produce a narrow zone of beta hemolysis around colonies and, therefore, are very similar to those of beta streptococci. If subcultured on nonenriched media the colonies become larger and rough. Organisms from rough colonies tend to be almost filamentous.

Antigenically, listeria is divided into 4 types on the basis of flagellar and somatic antigens. Five of these 8 strains were identified serologically by agglutination with polyvalent-O listeria antiserum. In the absence of specific antiserum, animal pathogenicity is of primary importance in the positive identification of listeria. Eighteen-hour broth cultures inoculated intraperitoneally in 0.2 ml. amounts into mice will kill the animals within 24 to 48 hours. Organisms are present in abundance in the liver and spleen. If the animals do not die too soon, areas of focal necrosis are visible grossly in these organs. Broth cultures should also be swabbed onto the conjunctiva of a rabbit's eye. A purulent keratoconjunctivitis begins to develop in about 48 hours and *L. monocytogenes* may be cultured from the exudate. The eye heals in 7 to 10 days, leaving no evidence of scarring but reinoculation will produce no infection. This reaction is diagnostically specific for *L. monocytogenes*. The

most important procedures used to identify the 8 cultures are summarized in Table 2.

Summary. Eight cases of listeria meningitis were admitted to the Communicable Disease Unit of the Los Angeles County Hospital within 4 years: 4 died and 4 completely recovered. All received penicillin and sulfa drugs, and all but one received chloramphenicol as initial therapy. Five of the 8 organisms were resistant to chloramphenicol, one was sensitive only to penicillin, and one was resistant to all antibiotics for which it was tested.

The bacteriology of *L. monocytogenes* is reviewed and the laboratory tests necessary for identification are emphasized.

Conclusions. Care must be taken not to identify *L. monocyogenes* falsely, either as a diphtheroid or as a beta streptococcus. All diphtheroids isolated from spinal fluids or blood cultures should be tested for motility in semi-solid medium incubated at room temperature. If motile, the organisms should be tested for virulence in mice and rabbits and serological identification done.

L. monocytogenes varies greatly in sensitivity to different antibiotics. *In vitro* sensitivity tests on the patient's organism are of great value as a guide to choice of individual therapy.

TABLE 2.—LABORATORY PROCEDURES USED IN IDENTIFYING 8 STRAINS OF *L. MONOCYTOGENES*

Strain	*Motility*	*Virulence in Mice*	*Kerato-conjunctivitis in Rabbits*	*Serology*
1.	+	+	ND	ND
2.	+	+	ND	ND
3.	+	+	+	+
4.	+	+	+	ND
5.	+	+	+	+
6.	+	+	+	ND
7.	+	+	+	+
8.	+	+	+	+

ND = Not done.

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(Interlingua on page 616)

PHYSICAL ACTIVITY: PERFORMANCE AND ATTITUDES OF A GROUP OF OBESE WOMEN*

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For several years investigations in the field of obesity have focussed on the caloric intake of obese persons and have demonstrated that caloric excess is often due to excessive food intake (Brosin[2], Bruch[3], Newburgh[11], and Rynearson and Gastineau[13]). Recently, however, the role of caloric expenditure as a factor in the pathogenesis of obesity has received increasing attention, and interest has shifted to the reciprocal effects of obesity and physical activity.

Bruch[4] was the first to call attention to the decreased physical activity of obese children. Since then Johnson, Burke and Mayer's[7] studies of obese adolescent girls have demonstrated underactivity of such degree that it appears more important than overeating in the development and maintenance of their obesity. These girls were far less apt to join in strenuous or competitive sports than nonobese classmates and preferred noncompetitive sports or sedentary activities. Mayer[8,9] has shown that the caloric surplus of obese-hyperglycemic mice during the active phase of their obesity is due primarily to the fact that they are far less active than their nonobese litter mates. When the "waltzing gene" is bred into this strain of mice, moreover, the resultant increased activity is sufficient to maintain a normal body weight.

The present study extends these investigations to a group of 15 obese women and compares their activity and attitudes toward activity with those of a group of 15 women of normal weight.

Methods. From the general medical clinic of the New York Hospital 15 obese women were matched in respect to age and occupation with 15 nonobese women. Neither group contained any person in whom illness might impede activity; the selection was otherwise a random one. The average percentage overweight of the obese women, as calculated from standard tables[12], was 62%, their average age was 42; the age of the control group averaged 40 years.

Physical activity was measured by a calibrated pedometer which each subject wore over her upper thigh for a period of one week. During the early part of the study only the mileage for the week as a whole was recorded. Later, to provide a measure of the day-to-day fluctuation, the mileage for each day was also measured.

The subjects' overt and covert attitudes toward activity were assessed by a direct questionnaire and by a specially devised sentence-completion test. Although this modification of the sentence-completion test has been described in detail elsewhere (Dorris,

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Levinson and Hanfmann[5], Hanfmann and Getzels[6], and Sacks[14]) its major features will be summarized. Its unique element is an assessment of the degree of self-awareness or insight of the respondent in relation to the response he has just given. This is derived by asking him, upon finishing the test, whether each completion which he has made is true of himself or not.

As administered in this study, the sentence-completion test consisted of fifteen paired, open-ended, moderately structured fragments, half of which used the first person pronoun, ("When I'm blue I . . .") and half of which used the third person pronoun, ("When she's down in the dumps she . . ."). After the subject had completed the test, she was instructed to reread each sentence and to decide whether it applied to her in any way. If she felt that it referred to any personal experience, or reflected the way she felt and acted or might feel or act under the given circumstances, it was given a positive rating. If the sentence had no application to the subject, the item was scored as negative. In this way a picture of the subject's conscious self-image was obtained, as well as her degree of acceptance of ego-alien material.

Pairs of sentences were analyzed and rated independently by 2 observers according to established criteria for 1) response to despondency, 2) response to boredom, 3) social interaction responses.

In analysis of the data presented here, a variety of tests of significance were used in an effort to utilize the one most appropriate to each problem (Snedecor[15]). Analysis of the activity measurements was carried out by means of Student's "t" test, considering the data in the form of a two-tailed distribution. Analysis of the direct questionnaires was carried out by means of the chi-square test. In treatment of the sentence completion test each sentence was considered a separate category, and the level of significance determined by calculation of the correlation coefficient.

Results. 1. PHYSICAL ACTIVITY. Pedometer measurements indicated that the obese women walked less than half as much as their nonobese controls. The mean weekly value for all obese subjects was 14.4 miles while that of the control subjects was 34.4 miles. Perhaps a more meaningful comparison is that of the matched pairs. In 14 out of 15 instances, the nonobese subject walked farther than the obese one by a difference which is significant at the 1% level. A summary of the weekly distance walked by each subject follows. Where available, a daily distance is included together with its standard deviation.

TABLE 1.—DISTANCES WALKED BY OBESE AND NONOBESE WOMEN (MILES)

	Weekly Distances			*Daily Distances*	
	Obese	*Nonobese*	*Difference*	*Obese*	*Nonobese*
	10.0	28.5	−18.5		4.1 ± 1.0
	23.0	17.5	+ 5.5	3.3 ± 0.8	2.5 ± 1.7
	11.0	19.5	− 8.5	1.6 ± 0.7	
	16.5	34.0	−17.5	2.4 ± 0.5	
	8.0	22.8	−14.8		3.3 ± 1.8
	7.8	16.5	− 8.7	1.2 ± 0.4	2.4 ± 0.3
	12.0	39.5	−27.5		5.6 ± 2.4
	10.7	23.0	−12.3	1.5 ± 0.5	
	24.0	31.4	− 7.4		
	8.3	30.5	−21.2	1.2 ± 0.4	4.4 ± 2.3
	5.5	64.5	−59.5		
	10.0	38.7	−28.7		
	10.2	61.7	−51.5		8.8 ± 1.2
	31.0	35.0	− 4.0		5.0 ± 1.5
TOTAL	14.4 ± 7.6	34.3 ± 14.5	−20.0 ± 16.2	1.8 ± 0.9	4.5 ± 2.5

Significant at the 1% level.

2. ANALYSIS OF DIRECT QUESTIONNAIRES. Each participant in the study was asked to estimate her activity on a four-point scale, and the estimates of each of the matched pairs was compared. In 8 cases the estimates of their own activity by the obese women were in accordance with actual performance; they were significantly lower than the self estimates made by the nonobese women. However, in the remaining 7 cases there was gross distortion. The estimate of activity made by the obese women was as great or greater than the self estimates made by nonobese women who were actually far more active.

	Obese More Active	*Nonobese More Active*
Actual performance	1	14
Estimated performance	7	8

Significant at the 5% level.

Analysis of the direct questionnaires indicated a trend which, although it did not reach statistical significance, is of interest. More obese than nonobese subjects expressed a preference for sedentary activities, and 5 of the 6 subjects who watched television more than 15 hours a week were in the obese group.

Two items which had been expected to differentiate the nonobese from the obese subjects revealed surprisingly similar attitudes in the two groups. First, all of the subjects stated that they ate less when they were busy, there being no apparent difference between obese and nonobese persons. The second similarity was in the amount of day-dreaming reported; here again there was no difference between obese and nonobese subjects.

3. ANALYSIS OF THE SENTENCE-COMPLETION TEST. A. *Response to despondency.* Physicians of obese persons have long noted their unusual susceptibility to depressive reactions (Stunkard[16]). Since a common characteristic of such reactions is psychomotor retardation, it seemed possible that this could play a role in the decreased activity of the obese women. Accordingly an attempt was made to assess the way in which the subjects of this study responded to feelings of depression.

The response of the obese women was strikingly different from that of their nonobese controls. Every one of the obese subjects reported a passive acceptance of depressive affects. For example, typical completions of obese women were: "When I'm blue I *just cry*" and "When she's down in the dumps she *just sulks*". The nonobese persons on the other hand, frequently gave responses which indicated an attempt to struggle against feelings of despondency. Typical of such responses were: "When I'm blue I *clean house*" and "When she's down in the dumps she *counts her blessings.*"

To summarize:

	Obese	*Nonobese*
Try to overcome mood	0	7
Passive acceptance of mood	14	7

Significant at the 5% level.

B. *Response to feelings of boredom.* In view of the frequency with which obese persons complain of boredom, it seemed important to determine how they evaluated their behavior in such circumstances. Again the results indicated a lesser degree of activity among the obese women than among their nonobese controls. Common responses by obese women were: "When I'm not interested I *get depressed*" and "When she's bored she *often shows it.*" Although some nonobese women gave similar responses, the majority indicated that they took a more active course in situations of boredom. Illustrative of this trend are typical responses by nonobese women: "When I'm not interested I *read*" and "When she's bored she *irons clothes.*"

To summarize:

	Obese	*Nonobese*
Active response to boredom	4	10
Inactive response to boredom	10	4

Significant at the 5% level.

C. *Social interaction responses.* Social interaction is a major stimulus to physical activity. It is, therefore, of interest that in reply to direct questions, 66% of the obese women said that they preferred to work with others, as compared with 38% of the nonobese women. However, when their capacity for social interaction was assessed by means of the sentence-completion test, the obese women were found to have significantly more social inhibitory and fewer social facilitatory responses than did the nonobese women. Thus, although the obese women seem to have a greater desire and presumably a greater need for easy relationships with others, they apparently have significantly less capacity to achieve these ends. Indicative of this trend are the following responses by obese subjects: "Working with people makes me feel *no different than working alone,*" and "The others in the office make her feel *isolated.*" Typical completions by nonobese subjects were: "Working with people makes me feel *just perfect*" and "The others in the office make her feel *welcome.*"

To summarize:

	Obese	*Nonobese*
More social facilitatory than social inhibitory responses	4	13
Fewer social facilitatory than social inhibitory responses	10	1

Significant at the 1% level.

D. *Insight.* The recent interest in psychosomatic aspects of obesity has resulted in the assessment of obese persons by psychological criteria. One of the most notable of these is insight. In the management of obese persons the internist no less than the psychiatrist has come to consider insight not only as a psychotherapeutic instrumentality, but also as a guide to the severity and prognosis of the disorder. Consideration of the rationale of this inference, or even of what is meant by insight, is clearly beyond the scope of this paper. However, the design of the sentence-completion test permits measurement of at least one component of what is traditionally considered insight.

As noted in the section on methods, immediately after finishing the test, each respondent was asked to reread each response and to indicate whether it applied to her in any way. Validation of this variation of the sentence completion test in earlier studies (Dorris, Levinson and Hanfmann[5], and Hanfmann and Getzels[6]) had indicated that the percentage of positive self-reference responses provided a rough measure of the subject's self-awareness or insight. Denial of self-reference, on the other hand, reflected defensive unawareness of one's unaccepted tendencies. It was possible to quantify this variable for each person by subtracting the total number of nonself-relevant responses from the total of self-relevant responses. Since there were 24 sentences in the test, each person could be rated along a scale with a theoretical range from +24 to −24.

Comparison of the self-awareness of the two groups revealed a most unexpected finding. There was no difference between the obese and the nonobese women. This was true both for comparison of the matched pairs and for comparison of the mean scores for each group. The latter findings, in fact, were identical: 14.1 ± 7.1 for the obese women and 14.1 ± 8.2 for the nonobese women.

Discussion. PEDOMETER STUDIES. This study was undertaken in an effort to investigate the role of physical activity in the energy economy of obese women. We believe that it is the first time that a direct measure of physical activity has been used in a study of this problem.* The value of such an effort seems obvious; its limitations should be considered.

Physical activity was measured by means of a New Haven Clock Company pedometer. This instrument responds to slight jolts by moving a carefully balanced arm. Thus, when the pedometer is worn over the upper thigh, each step taken during walking transmits an impulse to the balance arm. By calibrating the pedometer for the average length of the user's stride it is possible to convert such impulses into distances. Standardization of the equipment by one person walking a measured mile revealed that under these circumstances the results are remarkably accurate and that the variation from one instrument to the next is negligible. It is clear that impulses other than walking may disturb the balance arm and result in exaggeration of the distance walked. Such impulses, however, reflect the total activity of the wearer, and for the purposes of this study such a measure is at least as useful as that of actual distances walked. In interpreting the data it should be borne in mind that distances serve as an index of activity rather than a precise record of distances walked.

Use of this pedometer technique has revealed that a group of obese women were less than half as active as a similar group of women of normal weight. Conversion of these findings into a comparison of energy expenditure, however, presents serious difficulties. The greater weight of the obese women requires them to do more work than nonobese women in performing most types of physical activity. If translated into energy output, therefore, the apparently marked difference in physical activity between the two groups might well shrink to insignificance. Solution of this problem awaits more adequate instruments for the measurement of energy expenditure of human subjects.

ATTITUDE STUDIES. In searching for an explanation of the lesser activity of the obese women, the simplest hypothesis is that it is simply a result of their increased weight. The observation that obese women often become more active during the course of a successful weight reduction regimen provides anecdotal support for this view. At the present time we are investigating this possibility by means of long-term studies of obese persons, and by measurement of the activity of women who have at one time been obese.

An alternative view of the lesser activity of obese women would ascribe to this finding a role in the initiation or perpetuation of their obesity. If this were the case, characteristic attitudes toward physical activity might well differentiate obese from nonobese persons.

Analysis of the sentence completions of the group of obese women indicates that they may indeed be differentiated in this manner from a group of nonobese women. The obese subjects show a number of attitudes which may result in diminished physi-

*After this manuscript had been submitted for publication we learned of the excellent study of activity of obese persons by Gerhard Larsen in the "Tidsskrift for den norske laegforening," 17, 1, 1949. By the use of pedometers Larsen showed results very similar to those reported in the present study; 12 obese diabetic men and women over the age of 40 walked far shorter distances than did a control group of 10 nonobese persons.

cal activity. Faced with feelings of despondency, all of them responded by a passive acceptance; when bored, they tended to remain inactive. They indicated difficulties in interpersonal functioning of a type which may well restrict social interaction.

A word of caution about the results of the sentence-completion test is perhaps in order. It is important to recognize that the responses are statements about attitudes, not observations of behavior. And even the means of expressing the attitudes, for example, "response to feelings of despondency," is ambiguous in implying a distinction between feeling states and responses to them. Nevertheless these data indicate how the obese women viewed their own behavior. Inasmuch as such attitudes pattern behavior, they have predictive as well as symbolic significance.

One aspect of the obese women's attitudes towards physical activity is so strikingly similar to an attitude toward food intake that it deserves comment. It will be recalled that although many obese subjects thought of themselves as inactive and correctly estimated their activity at less than that of the control subjects, the estimates of others were grossly exaggerated.

This finding seems analogous to that reported by Beaudoin and Mayer[1] on the ability of obese women to estimate their food intake. They found that subjects of normal weight were able to estimate the caloric content of their food intake with considerable accuracy, and what errors they made were randomly distributed. The reports of the obese women, on the other hand, were in serious error, and these errors were always those of underestimation. These experimental findings confirm the clinical impression that many obese persons show distortions of perception or judgment of precisely those factors which contribute most heavily to their obesity. The function of this denial may be to make the obese person's activities appear more normal and less of an object of ridicule and self-recrimination. At the same time it materially increases the difficulties of consensual validation, and so, of successful treatment.

IMPLICATIONS FOR TREATMENT. The results of this study cast doubt upon the common view that increased activity is a futile gesture in the treatment of obesity. It seems clear that the physical activity of many obese women is so severely limited that even a modest increase might favorably alter caloric balance. No evidence has been adduced in favor of the oft-repeated argument that such increased activity automatically results in increased food intake, nor is there even a respectable theoretical basis for this contention. As Mayer, Roy and Mitra[10] have pointed out, such a sequence assumes a normal regulation of food intake, a curious assumption for an understanding of obesity.

The findings in regard to insight have further implications for treatment. As has been noted, internists as well as psychiatrists have come to view insight therapy as the method of choice in the treatment of obese persons. Yet this view is not supported by published reports indicating greater effectiveness of insight therapy and in the experience of one of the authors such treatment has not proved more effective than supportive, or relationship, therapy. This somewhat unexpected finding may be explained in at least two ways. On the one hand, obese persons may suffer from an ego defect which prevents adequate integration of unconscious material which has become conscious in the course of treatment. On the other hand, it may

well be that the defective performance of obese persons bears no relation to any lesser awareness of their motivations. Substantiation of this latter possibility would call for reconsideration of the current emphasis on insight therapy in the treatment of obesity. .

Summary. 1) A group of 15 obese women walked a significantly shorter distance over a period of one week than did a matched group of nonobese control subjects, as measured by a mechanical pedometer.

2) The attitudes toward physical activity of these women, as measured by direct questionnaire and sentence-completion tests, showed significant differences between the two groups. In situations of despondency and boredom, the obese persons commonly showed a passive acceptance of the situation in contrast to more active attempts at mastery by nonobese control subjects. Furthermore, despite the expression of a greater desire to participate in social interaction, the obese woman evidenced a lesser ability to achieve this goal.

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SUMMARIO IN INTERLINGUA

Activitate Physic: Performance e Attitudes de un Gruppo de Feminas Obese

1. Un gruppo de 15 feminas obese marchava in le curso de un septimana significativemente plus curte distantias, secundo mesurationes facite per medio de un pedometro mechanic, que un appareate gruppo de non-obese subjectos de controlo.

2. Le attitudes verso activitates physic, mesurate in iste feminas per medio de directe questionarios e tests a completion de phrases, revelava differentias significative inter le duo gruppos. In situationes de depression e enoio, le feminas obese monstrava in general un acceptation passive del cosas, per contrasto con le plus active effortios a maestrar los que characterisava le non-obese subjectos de controlo. In plus, in despecto de lor expression de un plus intense desiro de participar in interaction social, le feminas obese exhibiva un capacitate inferior de attinger iste objectivo.

SURVIVAL OF LUNG CANCER PATIENTS IN A GENERAL HOSPITAL POPULATION

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In recent years many authors have reported on large groups of patients with primary bronchogenic carcinoma treated in various metropolitan clinics and hospitals throughout the country (Churchill *et al.*[3], Gibbon *et al.*[4], Graham[5], Ochsner *et al.*[9], Overholt and Schmidt[12], and Rienhoff[13]). Most of these reports are concerned with patients referred directly to a thoracic clinic, and, therefore, deal with a selected population. For this reason it was felt that an analysis of patient material from a general hospital in a primarily agricultural state might present a different picture of some of the problems involved in the treatment of bronchogenic carcinoma and the length of patient survival. The University of Kansas Medical Center is a 600-bed general hospital situated on the eastern border of the State of Kansas. Each year it receives a large number of patients admitted to all services, referred for diagnosis and treatment by general practitioners from Kansas and three neighboring agricultural states. Thus it offers a fairly representative cross section of the major illnesses of patients in this part of the country.

Methods. Since 1948, all patients with the pathologic diagnosis of a malignant tumor established at this hospital have been recorded in a central tumor register, along with pertinent clinical information. Data on 5-year survivors with carcinoma of the lung, stomach, and prostate have been obtained for comparative study from this source. The few survivors with lung cancer were personally interviewed whenever possible and evaluated from the point of view of recurrence of tumor. Recent chest roentgenograms and a clinical evaluation were obtained from the family physician in other patients not followed at this hospital. All pathologic material on the survivors was reviewed in conjunction with the Department of Pathology and Oncology.

Results. In the 7-year period ending in 1955, 428 patients with primary bronchogenic carcinoma were studied at this hospital (Table 1). It will be seen that 91% of these patients were dead when this analysis was made, and that there were seven 5-year survivors, all of whom were surgical patients. There were no nonsurgical survivors.

The large number of patients found to be inoperable on initial evaluation (43%) is probably related to delay in evaluation inherent in the system of referring rural patients into the hospital, and is in keeping with the distressing picture presented by other authors (Ochsner, Dunlap and Richman[10]). Less than one-third of the total group of patients received some form of surgical therapy. Approximately two-thirds of patients operated were considered to be "curative" procedures, with at least the clinical expectation that all tumors had been removed. It was also noted in this review that, in recent years, the use of Roentgen irradiation and nitrogen mustard palliation of nonresectable tumors has increased, without any appreciable change in the duration of patient survival.

During this 7-year period there were 181 male patients seen with the diagnosis of carcinoma of the stomach, and 431 with prostatic carcinoma. An analysis of data presented in Table 2 compares patient survival with these commoner male tumors. In this series males with stomach carcinoma fared better than a larger group with lung cancer. Neither group, however, had nearly the survival rate as that seen in the males with prostatic malignancies. This may be related to the small number of urological patients deemed unsuitable for any form of therapy, but more probably represents differing host-susceptibility factors, and degrees of metabolic control of different tumors.

Figure 1 presents an analysis of age relationship of the three principal groups of tumors studied. In general, males in this series developed lung cancer at an earlier age than did patients in either the stomach or prostate groups. This factor is undoubtedly of further significance in evaluating the survival figures of older males with prostatic tumors. In the latter age group the attrition from nontumor entities, such as cardiovascular accidents and respiratory system infections, should be working to reduce further the number of 5-year survivors.

In considering the individual survivors, Table 3 shows that most had symptoms of relatively short duration. All the males were found to have central, obstructing, well-differentiated squamous-cell cancers, half of which were identified on bronchoscopic examination. The only female in this group had a peripheral anaplastic carcinoma that has not recurred, despite the limited resection performed. Two males had tumors that had metastasized regionally beyond the lung, despite which they have survived 7 and 8 years, free of recurrence of carcinoma. Five of the 7 survivors

TABLE 1.—ANALYSIS OF 428 LUNG CANCER PATIENTS AND THERAPY
K. U. M. C.
1948–1955

Total Patients	428	
Male	360 (84%)	
Female	68	
Dead	391 (91%)	*Five-year Survival* 7 (1.7%)
Treatment		
None	187 (44% of total)	
Surgery	126 (29% of total)	
Palliative	45[1]	
"Curative"	81 (64% of those operated; 19% of total)	
Roentgen-Irradiation	97[2] (25% of total)	
Nitrogen Mustard	15 (3.5% of total)	
Others	3	

[1]Combined with Roentgen-Irradiation 7
[2]Combined with Nitrogen Mustard 10

TABLE 2.—DATA ON COMMON MALE TUMORS
K U M C
1948–1955

	Lung	*Stomach*	*Prostate*
Total patients	360	181	431
% receiving "no treatment"	44%	33%	6%
Alive at time of study (patients)	31	22	152
5-year survivals (patients)	6	6	76

were age 60 or over at the time of operation; 4 of them have lived at least 5 years with only one lung.

Discussion. The over-all picture of surgical treatment of primary bronchial carcinoma remains a gloomy one (Mayer and Maier[7], and Rosenblatt and Lisa[14]). In certain selected series of patients, where surgery has been performed on asymptomatic and, it is hoped, early lesions, discovered by mass roentgenographic study of presumed "normal" populations, the results of lung resection have approched those expected for surgical treatment of other tumors (Overholt[11]). But, in general, the average incidence of operability, of resectability, and ultimate survival of large groups of patients differ little from those observed in this hospital in the period studied.

In considering surgical patients with lung cancer, others have noted a relationship between duration of symptoms, type and location of tumor, presence of metastases, and different surgical techniques employed and survival of those patients operated on (Brea[2], Churchill *et al.*[3], Moersch and McDonald[8] and Ochsner, Dunlap and Richman[10]). Again, these reports are in keeping with the observations noted in this group of patients derived from rural areas. It should be emphasized that the well-differentiated, centrally located, squamous-cell carcinoma carries the greatest chance for a reasonable surgical cure. This tumor may have metastasized outside the lung of its elderly subject, despite which a favorable prognosis can be expected in some. It should be remembered that the first pneumonectomy performed for lung cancer in 1933 by Dr. Evarts Graham on a fellow physician was for this type of tumor (Graham and Singer[6]). That well-differentiated squamous-cell carcinoma had already

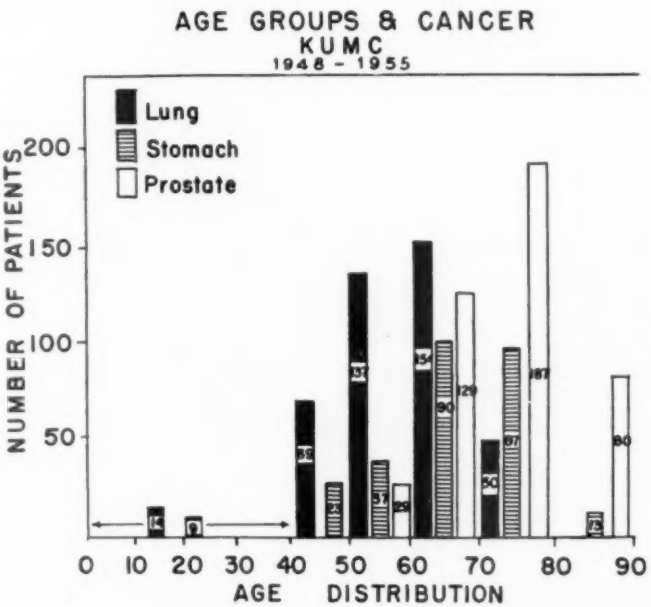

Fig. 1.—Age distribution of commoner male tumors.

TABLE 3.—CLINICAL DATA ON SURGICAL SURVIVORS
K.U.M.C.
1948—1955

Patient Age at Operation Race, Sex	*Duration of Symptoms*	*Occupation*	*Bronchoscopic Biopsy*	*Surgical Procedure*	*Tumor Classification*	*Reginal Lymph Node Metastases*	*Known Survival*
1. G.M., 43 yrs., W. ♂	1 Month	Warehouse Foreman	0	Left Pneumonectomy	Squamous Cell Ca.	+	7 Years
2. F.N.; 57 yrs., W. ♀	5 Months	Housewife	0	Rt. Lower Lobectomy	Anaplastic Cell Ca.	0	8 Years
3. C.T.; 60 yrs., W. ♂	3 Months	Farmer	+	Rt. Pneumonectomy	Squamous Cell Ca.	0	9 Years
4. J.L.; 60 yrs., W. ♂	6 Months	Farmer	+	Rt. Pneumonectomy	Squamous Cell Ca.	0	5 Years
5. H.G.: 60 yrs., W. ♂	2 Months	Farmer	0	Rt. Upper Lobectomy	Squamous Cell Ca.	0	7 Years
6. DB.; 64 yrs., W. ♂	3 Months	Clerk	+	Left Pneumonectomy	Squamous Cell Ca.	0	5½ Years
7. C.C.; 65 yrs., W. ♂	4 Months	Farmer	0	Rt. Pneumonectomy	Squamous Cell Ca.	+	8 Years

spread to regional lymph nodes, despite which the physican-patient continued his medical practice for more than 20 years (Ackerman[1]). This favorable survival of elderly males with this type of tumor treated by pneumonectomy underlines the concept that age in itself, should not be considered a contraindication to the surgical treatment of this malignancy.

Since surgical therapy today offers the only practical approach to prolongation of life for some lung cancer patients, or of cure for a few, it should be pursued in an aggressive fashion. It is disheartening to realize that despite an increasing awareness of the problem, and greater efforts at early case finding of asymptomatic lung cancer, the over-all survival results have improved so little in the past decade. This is undoubtedly due to the fact that the diagnosis of lung cancer continues to be primarily a radiological one, generally considered only when the invasive nature of the tumor suggests its presence with one of the manifestations of an advanced malignancy.

It is hoped that newer tests for biological activity of lung cancers will enable us to recognize the problem earlier, when today's surgical treatment has its greatest chance of cure. It can also be hoped that today's research into the causes and cellular chemistry of tumors will shortly give us a therapeutic tool better than our present palliative surgical one, and ultimately, the knowledge to prevent the majority of these malignancies.

Summary. A 7-year experience with some 400 lung cancer patients largely derived from a rural population has been described. It has been found to be very similar to experiences previously reported from metropolitan areas. Seven surgical patients survived at least five years of a postoperative observation period. Patients with well-differentiated, centrally located, squamous-cell carcinomas carried the best prognosis.

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(Interlingua on page 634)

SUMMARIO IN INTERLINGUA

Superviventia de Patientes de Cancere Pulmonic in un Population de Hospital General

Es describite le experientias colligite in le curso de 7 annos con alicun 400 patientes de cancere pulmonic recrutate principalmente ab un population rural. Esseva trovate que illos es multo simile al experientias previemente reportate ab areas metropolitan. Septe patientes chirurgic superviveva al minus cinque annos post le operation. Patientes con ben differentiate carcinomas a cellulas squamose e de location central habeva le melior prognose.

SUMMARIO IN INTERLINGUA

(See paage 603 for original article)

Manifestationes Clinic de Hypokaliemia

In le curso de un studio de 7 menses, 557 casos de hypokaliemia esseva incontrate in un total de 2786 determinationes de kalium. Le incidentia inter femininas esseva significativemente plus alte que inter masculos. Le mortalitate inter patientes hypokaliemic esseva frappantemente plus alte que le mortalitate inter le population hospitalari in general.

Cinquanta patientes hypokaliemic esseva seligite pro un evalutation detaliate. Plure factores etiologic que poteva esser responsabile pro le hypokaliemia esseva incontrate in quasi omne le casos. Alcalosis hypochloremic con hypocalciemia accompaniava communmente le carentia de kalium. Patientes con le plus basse nivellos de kalium del plasma habeva etiam le plus basse valores de calcium e chloruro del plasma e esseva plus alcalotic.

Le anormalitates clinic esseva del typo que es frequentemente incontrate in seriemente malade patientes con o sin hypokaliemia. Inter omne le anormalitates clinic, solmente le reducite activitate del reflexos tendinose profunde exhibiva un certe correlation con le reduction del nivellos de kalium plasmatic. Rapide infusiones de kalium esseva usate como methodo pro segregar le signos e symptomas inter illos constatate in le examine initial que esseva possibilemente le effecto de carentia de kalium. Le plus significative alterationes associate con infusiones de kalium esseva melioration del stato mental e augmento del activitate peristaltic. Altere phenomenos observate post plure dies de repletion de kalium esseva difficile a evalutar a causa del facto que varie procedimentos additional de therapia habeva essite executate. Le natura non-specific del manifestationes clinic de hypokaliemia in iste gruppo de seriemente malade e mentalmente obfuscate patientes sublinea le importantia de examines electrocardiographic e de altere technicas laboratorial in le diagnose de iste disordine.

RESPIRATORY INSUFFICIENCY AS A SYMPTOM OF CEREBELLAR ATAXIA

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The disturbance in the coördination of motor activity peculiar to cerebellar ataxia appears most clearly in connection with complicated motor performances. Cerebellar ataxia appears easily, especially in the movements which involve a quick alternation in the activity of antagonistic muscle groups (Goldstein[9], 1927; Bing[5], 1952). Respiration as a motor activity is a relatively complicated phenomenon (*cf.* Pitts[17], 1946). Therefore, it can be supposed that in cerebellar disturbances there will also be ataxic disturbances in respiration. The material here reported throws light on the influence of cerebellar ataxia on pulmonary function.

Material. The observations are based on 7 patients. The common factor in the cases was cerebellar ataxia. The etiology of this symptom showed a rather considerable variety in the different cases. Pulmonary function was examined with the help of spirometry.

Case Reports. CASE 1. Ataxic syndrome caused by a tumor of the cerebellum. The patient was a male, 60 years of age. At the age of 48, he had a surgical removal of a Lindau tumor of the left hemisphere of the cerebellum; recurrence of the tumor was operated upon at the age of 57. After this the symptoms did not disappear completely, sight was further weakened, and the ataxia, which was stronger in the left limbs, also became worse. The state of the patient progressed slowly to death. Postmortem examination showed a Lindau tumor of the left cerebellar hemisphere. There was necrosis of the left cerebellar hemisphere and of the left occipital lobe of the cerebrum, and a mild internal hydrocephalus. The clinical signs 3 months before death were: temporary vomiting, amaurosis, Romberg +, falling to the left. The ataxic disturbance of motor activity was rather slight in connection with simple movements, whereas the more complicated movements were greatly disturbed. Ataxic dysarthria appeared in the speech. The psyche was euphoric-anosognostic. The roentgenogram of the thorax was normal. Spirometry revealed a vital capacity of 1.86 L. (40% of normal), complementary air 0.37 L., tidal air 1.03 L., reserve air 0.46 L., and maximum breathing capacity 66 L./Min. (55% of normal). During the last month before death the patient had three rises of temperature to 39° C., due to bronchitis.

CASE 2. Ataxic syndrome caused by chronic misuse of carbromal. The patient was a 41-year-old male. When young, he was athletic. He had used carbromal daily from the age of 38, the daily dose being from 1½ to 6 gm. He was hospitalized for the first time 2½ years ago in a state of intoxication, giving the appearance of cerebellar ataxia. The condition improved in 6 days. During the two following hospitalizations, the condition was not wholly relieved even after prolonged treatment. Eight months ago, after the patient had taken 9 gm. of carbromal in the evening, motor activity was gravely disturbed the following morning. The patient could not rise from his bed and could not stand without help; his speech was almost unintelligible. He was placed in an institution for alcoholics. His condition after 2 months showed grave ataxic symmetrical disturbance of motor activity. Incoördination appeared even in the performance of a simple gesture, and walking was extremely difficult even with the help of a cane. The musculature was hypotonic, there was a static tremor and a strong ataxic dysarthria. Sensation was intact, the spinal fluid and electroencephalographic findings were normal. (For the general picture of carbromal intoxication *cf.* Magnussen[14], 1947.)

Radiography of the thorax was normal. Spirometry showed a vital capacity of 4.55 L. (89% of normal), complementary air 1.26 L., tidal air 1.53 L., reserve air 1.76 L., and maximum breathing capacity 73 L./min. (64% of the normal). During the following

year the patient was submitted to intensive physiotherapy, and his condition was improved to the extent that he was able to walk without a cane, and asynergy did not appear in a disturbing degree in slow movements. Repeat of spirometry showed vital capacity of 3.5 L. (69% of normal), complementary air 1.18 L., tidal air 1.22 L., reserve air 1.1 L., and maximum breathing capacity 62 L./min. (54% of normal).

CASE 3. Ataxic syndrome caused by chronic misuse of carbromal. The patient was a male, 53 years of age. He had had increasing insomnia during 8 years, and for this reason he used carbromal, first sporadically, now for about a year every other day from 1.5 to 3 gm., and abstaining generally in between. He began to suffer from headaches 3 years ago, felt very tired, had humming in the ears and tremor. The symptoms were alleviated by a course of treatment for anemia, but then became worse again. For the past 6 months, the patient has been in very poor condition, and has lost 10 kg. in weight. For the past 6 weeks he has been unable to attend to his work because of shortness of breath and easy fatigability. During the last few days before he was taken to the hospital the patient was confused, the use of carbromal being then probably much larger than stated above. When taken to the hospital the patient was cachectic, lean, and extremely somnolent. He had a coarse tremor of the hands, a positive Romberg sign, and muscular strength generally much diminished; motor activities, including speech, showed an ataxic disturbance.

The patient was coughing. The lungs were hyperresonant. Radiological appearance of the lungs was slightly emphysematous, and the apices showed alterations due to tuberculosis. In a radiologic study of the chest, these alterations proved nonactive. In a radiogram of the thorax to which the patient had been submitted 4 years earlier, these alterations were not to be seen in the apices of the lungs. Spirometry, made after the general condition of the patient had improved as a result of a 2-weeks' treatment in the hospital showed a vital capacity of 4.62 L. (100% of normal), complementary air 1.42 L., tidal air 1.25 L., reserve air 1.95 L., and maximum breathing capacity 69 L./min. (63% of normal).

CASE 4. Arteriosclerotic parkinsonism with strong cerebellar and bulbar symptoms. The patient was a male, 52 years of age, who had had malaria when 39. From the age of 45 on the legs have felt more and more stiff, capacity for ambulation and speaking have deteriorated. He has been unable to work from the age of 50 on. His blood pressure was 230/145 mm. Hg. There was hypertrophy of the left ventricle of the heart; sclerosis of the aorta; bilateral hearing impairment of mixed type; central left-sided facial paralysis, right-sided abducens paresis. Sensation was intact. Muscular strength was diminished throughout, more on the left side, and the left limbs were slightly atrophied. The tendon reflexes were more active on the left. Babinski was mildly positive, more on the left. Adiadochokinesis was present, more strongly on the left side. There was advanced generalized rigidity, the expression of the face was waxy, there were difficulties in opening the mouth, swallowing, coughing and breathing; there was occasional dyspnea even at rest. The voice was hoarse; speech, indistinct, slow and stiff. There was a static tremor in all the limbs. Movements were stiff and ataxic. The patient showed emotional lability, was restless during the nights and complained of a weakening of memory. Air-encephalography showed the ventricular system considerably distended, especially the left ventricle and the aqueduct, especially near the 4th ventricle. The lungs, with the exception of a slight stasis, showed nothing unusual. Spirometry showed a vital capacity of 0.82 L. (19% of normal), complementary air 0, tidal air 0.82 L., reserve air 0, maximum breathing capacity 15 L./Min. (15% of normal).

CASE 5. Ataxic syndrome following an apoplectic insult (cerebellar hemorrhage?). The patient was a male, 66 years of age. When 50, he had had a left-sided hemiplegia induced by a strong muscular effort. Simultaneously, a strong tremor appeared in the whole body, as well as uncertainty of movements, unsteadiness of posture and speech difficulty. The left-sided hemiplegia improved so far as to leave almost no symptoms, but the other symptoms remained. The patient was lean, the muscular strength was slightly diminished throughout, more on the left side; the left limbs showed a slight atrophy. The musculature was hypotonic. There was a left-sided hemihyperesthesia and a positive Romberg. The motor activity showed a considerable ataxic disturbance, so that the patient, for example, could not eat by himself. The whole body showed a strong coarse static tremor, and there was also tremor, with the same rhythm in the soft palate and the vocal cords. Speech was very indistinct. The patient showed emotional lability; the intellectual functions worked rather well.

The lungs were slightly hyperresonant. The radiological appearance of the lungs was slightly emphysematous. Spirometry showed a vital capacity of 3.25 L. (66% of normal), complementary air 2.38 L., tidal air 0.54 L., reserve air 0.33 L., and maximum breathing capacity 39 L./min. (35% of normal). During a 2-months' stay at the hospital, there was twice a sudden rise of temperature to 39.5° C., due to bronchitis.

CASE 6. Ataxic syndrome following a subarachnoidal hemorrhage. The patient was a male, 40 years of age. When 37, he had a fainting attack in a skiing competition, and after this the speech was difficult for 24 hours. After 4 months there was a sudden fit of unconsciousness, repeated vomiting, inequality and immobility of pupils, and the spinal fluid was evenly bloody. Forty-eight hours later there was a considerable amount of old blood in the spinal fluid. After this, the patient was confused for about a month. As a permanent consequence, there was a strong emotional lability and an ataxia which appeared only slightly in connection with simple movements, but very strongly in connection with complicated motor performances. Walking was extremely difficult and the speech was also ataxic to a considerable degree. In the air-encephalogram the right side ventricle appeared slightly distended. Bilateral carotid and vertebral angiographies were normal.

The radiological appearance of the lungs was normal. Spirometry showed a vital capacity of 4.7 L. (112% of normal), complementary air 3.81 L., tidal air 0.72 L., reserve air 0.17 L., and maximum breathing capacity 71 L./min. (51% of normal). Maximum expiration capacity was 124 L./min. (90% of normal). Total capacity was 5.67 L. (107% of normal), residual air 1.7 L., residual air in % of the total capacity = 20% (normal = 23%).

CASE 7. Ataxic syndrome, the etiology of which remained unclear. The patient was a male, 60 years of age. At the age of 54, the legs began to weaken and walking became uncertain. The symptoms became slowly stronger, and the same symptoms, though less marked, appeared also in the hands. Now, in a year's time, the speech had become difficult, and intermittent difficulties in breathing appeared. The patient was lean and looked much older than his age. Motor activity was affected throughout by a grave ataxic disturbance, which appeared clearly even in connection with simple movements, and made more complicated motor performances impossible. The ataxia was stronger in the right limbs and much stronger in the lower than the upper limbs. Babinski was +. There was slight spasticity in the right upper limb. Radiography of the neck showed considerable degenerative changes in the whole cervical column. The electroencephalogram, pneumoencephalogram and spinal fluid were normal.

The patient suffered from intermittent dyspnea even at rest, which was temporarily relieved by lobeline. The excursions of the chest were diminished; especially inspiration was difficult and spastic. The breathing space (between the vocal cords) was only 4 mm. The radiological picture showed increased lung markings, changes due to old tuberculosis in the hilar areas and in the mid-zones. (Before the present illness, the patient had twice suffered from pneumonia.) Spirometry showed a vital capacity of 2.09 L. (59% of normal), complementary air 0.77 L., tidal air 0.64 L., reserve air 0.68 L., and maximum breathing capacity 32 L./min. (35% of normal.) Maximum expiratory capacity was 66 L./min. (72% of normal), total capacity 4.4 L. (86% of normal), residual air 2.31 L., residual air in % of the total capacity was 53% (normal = 31%). The patient had a chronic bronchitis, maintained no doubt by the deficient ventilation. The general state of the patient became steadily worse and breathing became more and more difficult. Death occurred after 6 months, preceded by prolonged rises in temperature against which penicillin was of no use, lobeline being, on the contrary, efficient. The patient died at home in a rural district; there was no postmortem examination.

Results. The results of spirometry in Table 1 show that in our patients pulmonary function was considerably impaired. The vital capacity had been reduced by one-third, due almost exclusively to the decrease of complementary air. Reserve air had also been reduced in a slight degree. Thus the relative part of tidal air in vital capacity is considerably larger than normally (*cf.* Baldwin, Cournand and Richards[2], 1948, Tala *et al.*[19], 1954). The maximum breathing capacity was only a half, or slightly less, of the normal. The maximum breathing capacity is thus relatively still more disturbed than vital capacity. This also conforms

to the character of an adiadochokinetic disturbance, since the defects due to an asynergy of the musculature are emphasized during continuous rapid maximum breathing. The fact that complementary air has been relatively more reduced than reserve air shows that active inspiration has become more difficult than active expiration. In the two cases in which the maximum expiratory capacity was also determined, it was stated that it was considerably less reduced than the maximum breathing capacity. These results point to the conclusion, that the diminution of the maximum breathing capacity is principally due to disturbance of inspiration.

The motor activity of the patients was in the majority of cases rather limited on the basis of grave ataxic disturbances. Because of this, the untoward effects of a respiratory insufficiency did not appear in all the cases, even though this insufficiency was considerable. In 2 cases, respiratory insufficiency was, however, so marked that dyspnea was observed at rest. (In one of these cases insufficient respiration was due, not only to ataxia but to other central factors; Case 4.) In one of these patients the insufficient ventilation of the lungs was obviously responsible for a chronic bronchitis. It is also obvious that in this case the insufficient respiration hastened death. In addition, 2 more patients showed a tendency to infections of the respiratory tract (Cases 1 and 5). In one of the cases in which the ataxic syndrome was due to chronic misuse of carbromal (Case 3), it was stated that the patient had had a tuberculous infection at the apices of both the lungs.

Discussion. Until now little attention has been paid to respiratory insufficiency due to cerebellar ataxia. This has probably been due to the fact that, in the cases in which ataxia has been

TABLE 1.—RESULTS OF SPIROMETRIC STUDIES IN A GROUP OF 7 PATIENTS WITH CEREBELLAR ATAXIA

Subject	*Vital capacity*		*Complementary air*		*Tidal air*		*Reserve air*		*Maximum breathing capacity*	
	L.	*% of normal*	*L.*	*% of vital capacity*	*L.*	*% of vital capacity*	*L.*	*% of vital capacity*	*L./min.*	*% of normal*
1	1.86	40	0.37	19.9	1.03	55.4	0.46	24.7	66	55
2	3.5	69	1.18	33.7	1.22	34.8	1.1	31.5	62	54
3	4.62	100	1.42	30.8	1.25	27	1.95	42.2	69	63
4	0.82	19	0	0	0.82	100	0	0	15	15
5	3.25	66	2.38	73.2	0.54	16.6	0.33	10.2	39	35
6	4.7	112	3.81	81.1	0.72	15.3	0.17	3.6	71	51
7	2.09	59	0.77	36.8	0.64	30.6	0.68	32.6	32	35
Mean value	2.97	66	1.42	48	0.88	30	0.67	22	50	44

so strong that it has caused a considerable respiratory insufficiency, motor activity as a whole has been mostly very gravely impaired. This general ataxic disturbance makes it difficult to observe the respiratory insufficiency. It can, however, be mentioned that Cournand, Brock, Rapport and Richards[6] (1936) have investigated dyspnea caused by functional disturbances of the breathing muscles. Cases of grave cerebellar syndromes in which infection of the respiratory tract has caused death have also been reported in the literature (Hunter and Russel[13], 1954). The results mentioned above point to the fact that cerebellar ataxia creates a predisposition for infections of the respiratory tract. In the light of this evidence, it seems possible that, in the cases mentioned in the literature, respiratory insufficiency should have produced a predisposition to infection of the respiratory tract.

Compared to the spirometric picture characteristic of the various forms of a peripheral ventilatory insufficiency (Baldwin, Cournand and Richards[3,4], 1949; Motley, Lang and Gordon[16], 1949; Gray[10,11], 1950; Helmholz[12], 1952; Motley[15], 1952; Schmidt[18], 1952), central ataxic respiratory insufficiency is characterized, in the light of the results set forth above, especially by a decrease of complementary air and maximum breathing capacity. The effect of cerebellar asynergy is considerably more injurious on the maximum breathing capacity than on the vital capacity. This observation gives support to the view, which has often been expressed, that the vital capacity and the maximum breathing capacity are in part dependent upon different factors (Cournand, Richards and Darling[7], 1939; Gilson and Hugh-Jones[8], 1949; Astrand[1], 1952).

The material here reported is too limited to allow a detailed elucidation of the importance of cerebellar factors in pulmonary function. The results obtained show, however, that there are good reasons to examine the question more thoroughly.

Summary. Respiratory insufficiency due to cerebellar ataxia was studied in 7 patients. There was observed a considerable disturbance of pulmonary function, characterized by a decrease of complementary air and especially of the maximum breathing capacity. The respiratory insufficiency obviously produced a tendency to infections of the respiratory tract. These results warrant further investigation of the condition.

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SUMMARIO IN INTERLINGUA

Insufficientia Respiratori Como Symptoma de Ataxia Cerebellari

Insufficientia respiratori debite a ataxia cerebellari esseva studiate in 7 patientes. Esseva observate un considerabile disturbation del function pulmonar, characterisate per un reduction del aere complementari e specialmente del capacitate respiratori maximal. Le insufficientia respiratori resultava obviemente in le tendentia a infectiones del vias respiratori. Iste resultatos justifica studios additional del condition.

SUMMARIO IN INTERLINGUA

(See page 641 for original article)

Relation Inter Numerationes Chylomicronic e le Fractionation per Ultracentrifugation del Lipidos Seral

1. Post un repasto grasse, heparina e mepesulfato es ambes capace a alterar significativemente e intra un periodo de 30 minutas le fractiones de flottation Svedberg e le nivello de lipomicronemia. Un grado de supression proportionalmente plus marcate occurreva in le lipomicronemia que in ulle del fractiones de flottation. Le alte fraction lipidifere Sf 35 a 100 esseva supprimite plus regularmente que le fractiones Sf 12 a 20 o Sf 20 a 35.

2. Mepesulfato administrate diurnemente durante 4 dies induceva in 4 ex 8 patientes un fin emulsification de lipidos visibile in le campo nigre e reduceva significativemente omne fractiones de flottation Svedberg. Heparina non produceva le mesme effecto. In le patientes individual, le grado del alteration in emulsification esseva parallel al alteration del fractiones Sf 12 a 20 e Sf 20 a 35 sed non Sf 35 a 100.

3. In le 10 patientes (7 tractate con mepesulfato e 3 tractate con heparina) qui monstrava significative alterationes del emulsification de lipidos visibile in le campo nigre, un concentration augmentate del fraction Sf 12 a 20 in comparation con le fraction Sf 35 a 100 esseva associate con augmentate grados de emulsification. In un sol caso le augmento del fraction Sf 35 a 100 excedeva le augmento del fraction Sf 12 a 20, e in iste caso un reduction del grado de emulsification esseva notate.

4. Le datos indica que determinationes del indice de chylomicrones reflecte qualitativemente le alterationes del fractiones lipoproteinic que plus exacte methodos defini quantitativemente.

INTERRELATIONSHIP OF CHYLOMICRON COUNTS AND ULTRACENTRIFUGE FRACTIONATION OF SERUM LIPIDS*

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The objective of this study was to learn if simple chylomicron counts and estimation of variations in chylomicron size were related to the more complex Svedberg flotation fractionations as reflected by heparinoid effects. Gofman *et al.*[6] have stated that there is no apparent relationship between chylomicrons and the Sf 12–20 ultracentrifuge fraction. Their view, based on ultracentrifuge rather than on dark-field microscopic studies of the chylomicra, was in accord with known data in 1950. Chylomicra have a high neutral fat content, large size, low density, and increase massively after fatty meals. This is in direct contrast with the high lipoprotein and cholesterol content, molecular size, and higher density of Sf 12–20 particles which are unaffected by postprandial lipemia. A precise definition of the chylomicron is a lipid globule 0.3 micron or larger (Gage and Fish[5]). Since lipid globules as small as 35 millimicrons in size may be accurately measured, Frazer and Stewart employed the term lipomicron to include all lipid globules (Frazer and Stewart[4]). By the nature of its preparation the "chylomicron" layer referred to by Gofman represented neutral fat from particulate material of undetermined sizes; thus the suggestion that this was a "chylomicron" fraction was misleading, when considered in terms of the definition of chylomicron as established by Gage and Fish[5] and amplified by Frazer and Stewart[4].

The chylomicron index (per cent of dark-field-visible lipid 0.3 micron or larger in diameter) is one measure of the degree of lipid emulsification in fasting serum. The presence of a globulin-like protein in the monolayer about the chylomicra was demonstrated by Elkes, Frazer and Stewart[2]. That beta lipoprotein is an integral part of chylomicra was shown by Middleton[8]. Byers and Friedman[1] have indicated that almost all the exogenous cholesterol exists in these globules. What were once conceived to be neutral fat

*This study was supported in part by grants from the Los Angeles Heart Association and Hoffman-La Roche, Inc. The Svedberg determinations were done by Mr. Colovos at the Research Laboratories of The Upjohn Company.

A preliminary report of this study was given in "Comparison of chylomicrons with ultracentrifuge fractions and effect of heparin and a synthetic heparinoid" by **Field, J. B., Zinn, W. J., and Griffith, G. C.:** Fed. Proc., **13**, 688, 1954.

globules are now believed to be complex lipoprotein aggregates with high neutral fat content. The existence of an inverse relationship between protein content and lipomicron size has been supported by Weld[9]. Protein content is related to particle size and the protein of lipomicra exists at the surface monolayer. Thus variations in specific lipoproteins may be reflected by alterations in particle size. To explore this possibility, comparison of Svedberg flotation fractions, total lipomicron counts, and chylomicron indices was undertaken.

Method. First an evaluation was made of the immediate response of the Svedberg flotation fractions 12–20, 20–35, 35–100, and lipomicronemia to intravenous heparin (100 mg.) and mepesulfate* (500 mg.) administered three hours after a 20 gm. fat meal in a manner as previously described (Field *et al.*[3], Zinn *et al.*[10]). Eleven subjects were given first one medication and, after a 2-day interval, the other. To eliminate bias, alternative subjects were given heparin or mepesulfate. The fasting, 3-hour post-cibum, and 30-minute post-medication samples were tested. Previous studies with the 20 gm. fat meal had demonstrated that between 3 and 3½ hours post-cibum either a continued rise or an insignificant fall in lipomicronemia might be expected (Zinn and Griffith[11]).

Secondly, observations were made on changes in fasting serum flotation fractions and chylomicron indices after 4 days of intramuscular administration of heparin or mepesulfate in the same doses to 17 subjects. Again subjects were started alternately with heparin or mepesulfate. Following each 4-day course, and after the appropriate measurements were made, a 2-day interval was allowed before the medications were switched.† Fasting samples were obtained prior to each course of therapy and again on the morning following the last injection. Injections were given each morning during the course of treatment.

Svedberg flotation fractionation was performed by the method described by Gofman and associates[6]. The chylomicron index and total lipomicron counts were performed as previously described (Field *et al.*[3], Zinn *et al.*[11]). In brief, capillary tubes of arterialized finger capillary blood were centrifuged and counts made of the lipomicrons and chylomicrons by dark-field examination. The subjects received a fat-free meal the night before sampling, and were fasting between midnight and the 8 A.M. sample.

The project technicians knew samples only by code numbers. The accuracy of individual determinations was checked by frequent duplicate determinations.

Results. Duplicate determinations on 12 samples of each Svedberg flotation fraction showed a maximum variation of 8 mg., 11 mg., and 12 mg. per 100 ml. respectively for the Sf 12–20, 20–35, 35–100 molecules; mean variations of 5 ± 3, 5.5 ± 4, and 4 ± 4.5 mg. per 100 ml. were found for the respective determinations. Three times these standard deviations (a probability of 1:370 for chance occurrence) were arbitrarily considered as evidence of a significant change in the flotation fractions. A shift in lipomicronemia exceeding 200 globules per 100 fields met the above criteria as did a shift of over 7% in the chylomicron index.

Table 1 shows the immediate changes noted in lipemic serum from each subject following the intravenous injection of heparin or mepesulfate at the height of the postprandial lipemia. Significant Sf 12–20 changes occurred in 7 heparin-treated, and 4 mepesulfate-treated subjects. Two showed a rise

*Mepesulfate is the generic designation of the sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside developed in the laboratories of Hoffmann-La Roche, Inc., Nutley, N. J., and furnished by Dr. Leo A. Pirk.

Heparin was furnished in generous quantities through the courtesy of The Upjohn Company, Kalamazoo, Mich., and Hoffmann-La Roche, Inc., Nutley, N.J.

†This corresponds to the prolonged effect of mepesulfate as an anticoagulant when given intramuscularly. A dose of 500 mg. has maintained whole blood clotting times at more than twice normal after 30 hours whereas the effect of 100 mg. heparin is dissipated in about 10 hours (Field *et al.*[3]).

TABLE 1.—CHANGES NOTED IN LIPEMIC SERA AFTER INTRAVENOUS ADMINISTRATION OF HEPARIN AND MEPESULFATE IN 11 PATIENTS.

Heparin 100 mg.							*Mepesulfate 500 mg.*							
*3-hr. post-cibum**				*½-hr. post-heparin*			*3-hr. post-cibum**				*½-hr. post-mepesulfate*			
Sf 12–20 mg./ 100 ml.	*Sf 20–35 mg./ 100 ml.*	*Sf 35–100 mg./ 100 ml.*	*Lipomicrons per 100 fields*	*Sf 12–20 mg./ 100 ml.*	*Sf 20–35 mg./ 100 ml.*	*Sf 35–100 mg./ 100 ml.*	*Lipomicrons per 100 fields*	*Sf 12–20 mg./ 100 ml.*	*Sf 20–35 mg./ 100 ml.*	*Sf 35–100 mg./ 100 ml.*	*Lipomicrons per 100 fields*	*Sf 12–20 mg./ 100 ml.*	*Sf 20–35 mg./ 100 ml.*	*Sf 35–100 mg./ 100 ml.*	*Lipomicrons per 100 fields*
20	12	8	800	4	6	4	158	22	6	1	950	9	5	6	154
43	34	43	870	24	6	2	74	39	31	32	1260	56	19	11	265
35	31	32	1320	22	5	1	400	33	29	20	880	21	3	1	350
30	39	60	1260	35	13	10	175	32	27	26	900	19	7	4	370
34	19	32	440	30	80	11	240	37	18	19	850	47	14	5	230
56	74	133	350	89	43	18	80	92	91	144	495	118	59	14	262
35	20	26	1005	7	3	Tr.	52	12	9	4	980	10	4	Tr.	790
45	23	38	655	65	11	5	144	61	37	68	655	62	29	3	630
37	16	2	1050	8	3	2	174	44	24	5	1250	21	5	Tr.	840
53	47	28	1180	52	6	7	310	60	48	55	1120	57	21	4	480
32	23	13	1833	9	1	Tr.	160	27	12	24	800	2	1	Tr.	184

* Taken just before administration of drug.

after heparin, the remainder showed a fall. The Sf 35–100 particles were significantly altered in 8 heparin-treated, and 7 mepesulfate-treated subjects. Here all shifts consisted of reductions in concentration following medication. In 6 of the 7 remaining trials the initial level was too low to permit evaluation. In the seventh subject no flotation fraction shifted significantly with mepesulfate. The Sf 20–35 particles showed substantial variation in 7 heparin-treated and 3 mepesulfate-treated subjects. In one of these, a significant rise occurred following heparin administration. Postprandial lipemia was reduced significantly in 20 of the 22 trials. In one of the two unaffected no fraction was particularly altered. In the other Sf 12–20 and 20–35 fractions were unaffected but the Sf 35–100 fraction was sharply reduced.

Thus, the lipomicronemia and the Sf 35–100 fraction were both sharply reduced by the two anticoagulants. The Sf 12–20 fraction shows no consistent response; indeed the response of the Sf 12–20 and Sf 20–35 fractions to the intravenous administration of these anticoagulants was insignificant in 50% of the observations made 30 minutes after drug administration. When diminished concentrations alone were considered, significant shifts occurred in 32% of the Sf 12–20 determinations, 41% of the Sf 20–35, 68% of the Sf 35–100, and 91% of the lipomicron counts.

The effect of 4 days of medication with these two anticoagulants on fasting lipid constituents is shown in Table 2. Significant alterations are noted in the table. Four of the 8 mepesulfate-treated subjects had substantial alterations in all fractions. These are given in order of the magnitude of the shift encountered in Table 3. On a scale of 1 to 4, the maximum alteration is represented by 1, the minimum by 4.

Discussion. As previously noted (Field *et al.*[3], Zinn *et al.*[11]) within 30 minutes of heparin or mepesulfate administration there results a uniform reduction of lipomicronemia. No difference was noted in the effect of the two compounds on Svedberg flotation fractions. Within 30 minutes both compounds sharply reduced the lipomicronemia and the Sf 35–100 fractions. Effects on the small Sf fractions 12–20 and 20–35 were not consistent. This appears to be proportionate to the relative degree of neutral fat content of each fraction, for the highest lipid-lowest protein containing fraction (Sf 35–100) should most closely parallel the shifts of the high fat-low protein lipomicra. Both heparin and mepesulfate showed early effects most strikingly on these labile lipid constituents. The lipomicronemia sensitively reflected the clearing factor effect of both heparin and mepesulfate. Due to the density of the lipemia no observation on particle size alteration was possible during the absorptive period.

The second portion of the study was directed specificially at the emulsifying effect of heparin and mepesulfate. The data show that in the doses used heparin had no significant lipid effect 24 hours after the last dose. Mepesulfate did exert a definite activity 24 hours after the final dose. In 4 of the 8 mepesulfate-treated subjects all fractions were altered beyond the limits of insignificance. Here the degree of change in emulsification as noted in Table 3 was parallel with the degree of alteration in Sf 12–20 and Sf 20–35 fractions. The labile Sf 35–100 fraction was markedly reduced in three of the four instances. The parallelism between the degree of emulsification of the lipomicra and the alteration of the more dense Sf fractions supports the possibility that the protein monolayer coating lipomicra may contain variable quantities of the Svedberg flotation fractions.

Where medication increased the emulsification (that is, decreased the chylomicron index) the relative amounts of Sf 12–20 were increased compared to the Sf 35–100 fraction. This was true in spite of significant absolute reductions

Although this study has been limited in scope due to the small proportion of the total lipoprotein ultracentrifugal spectrum evaluated, the findings suggest that variations in the concentrations of ultracentrifugal moieties

TABLE 2.—CHANGES INDUCED IN FASTING LIPID CONSTITUENTS AFTER 4 DAYS OF HEPARIN OR MEPESULFATE

Subject	*Chylomicron Index* Before	Sign.*	After	*Sf 12–20* Before	Sign.*	After	*Sf 20–35* Before	Sign.*	After	*35–100* Before	Sign.*	After
Mepesulfate in 8 subjects												
A.	43	No	42	78	Yes	50	66	Yes	8	73	Yes	1
H.	31	Yes	20	61	"	18	38	"	2	37	"	Tr.
T.	37	"	24	80	"	27	37	"	4	55	"	Tr.
B.	46	"	23	44	"	3	31	"	1	37	"	Tr.
N.	42	"	22	15	No	7	5	No	1	1	No	Tr.
D.	50	"	43	44	Yes	22	45	Yes	22	108	Yes	24
M.	46	"	37	38	No	29	26	No	16	27	"	8
M.	39	"	32	37	"	28	23	"	13	34	"	2
Heparin in 9 subjects												
T.	30	Yes	40	36	No	23	10	No	15	5	No	10
W.	38	No	36	36	"	34	18	"	27	27	Yes	61
M.	44	"	38	28	"	26	7	"	13	2	No	7
H.	41	"	42	34	"	44	19	"	29	19	"	30
B.	51	Yes	29	38	"	45	28	"	21	18	"	19
W.	46	"	35	38	"	33	28	"	17	46	Yes	41
R.	31	No	28	27	"	30	10	"	8	17	No	19
A.	56	"	51	70	"	74	28	Yes	52	8	Yes	40
S.	42	"	43	74	"	66	33	No	32	36	No	41

*Significance.

TABLE 3.—MEPESULFATE-INDUCED ALTERATIONS IN ORDER OF MAGNITUDE; FROM DATA OF 4 SUBJECTS GIVEN IN TABLE 2

Subject	*Chylomicron Index*	*Sf 12–20*	*Sf 20–35*	*Sf 35–100*
B.	1	1	1	1
H.	2	2	2	1
T.	3	3	3	1
D.	4	4	4	2

in the concentration of the Sf 12–20 fractions. In the one instance (T.), when emulsification decreased (a greater proportion of large globules was present), the relative proportion of Sf 12–20 to Sf 35–100 particles decreased despite an insignificant reduction in the absolute concentration of the Sf 12–20 fraction.

influence the emulsification of the naturally occurring fat and protein complexes comprising the dark-field-visible lipomicra. Two practical points have emerged. Variations in total lipomicron counts reflect effects upon the triglyceride complexes and do not relate consistently to the higher density Sf 12–20 lipoproteins. Lipomicron size

variations as judged by the proportionate shift of chylomicron concentration (chylomicron index) are related to Sf 12–20 alterations. Increased protein content was associated with increased emulsification (lower chylomicron index).

Conclusions. 1. After a fat meal, both heparin and mepesulfate significantly alter Svedberg flotation fractions as well as lipomicronemia within a 30-minute period. Lipomicronemia was proportionately suppressed more than any flotation fraction. The high lipid-containing Sf 35–100 fraction was more consistently suppressed than the Sf 12–20 or Sf 20–35 fractions.

2. Mepesulfate given daily for 4 days induced a fine emulsification of dark-field-visible lipids and significantly reduced all Svedberg flotation fractions in 4 of 8 patients. Heparin did not have this effect. In these patients the degree of alteration of emulsification paralleled the change in Sf 12–20 and Sf 20–35 fractions, but not the Sf 35–100 fraction.

3. Among the 10 subjects (7 mepesulfate-treated, 3 heparin-treated) who showed significant changes in emulsification of dark-field-visible lipids, increased concentration of the Sf 12–20 fraction with respect to the Sf 35–100 was associated with increased emulsification. In the one instance where the Sf 35–100 fraction rose more than the Sf 12–20, decreased emulsification was noted.

4. The data indicate that determination of the chylomicron index will reflect in a qualitative manner the quantitative shifts in lipoproteins noted by more exact techniques.

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(Interlingua on page 640)

A CLINICAL STUDY OF ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION WITH PARTICULAR REFERENCE TO EARLY HEPARIN THERAPY*

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The use of anticoagulant drugs in the management of patients with acute myocardial infarction unfortunately is still an unsettled question in the minds of many competent physicians. The repeated surveys of the problem fail to reveal any unanimity of opinion due in part to different methods of approach and selection of material. Though many studies have been conducted concerning the use of Dicumarol few have indicated the value of supplemental heparin in the early phase of anticoagulant therapy.

This study was undertaken to evaluate our own experience with anticoagulant therapy and to determine if the early use of heparin was a beneficial supplement to Dicumarol. It represents the experience in a university hospital serving a community with both ward and private patients under the control of competent physicians with a good general laboratory capable of satisfactory prothrombin determinations.

The decision concerning the use of anticoagulants rested with the attending physician and the attitudes concerning this changed slightly from year to year, thus possibly influencing the type of patients admitted to the hospital for treatment.

Four hundred and seventeen cases of myocardial infarction were admitted to the University Hospital between January, 1947, and December, 1955, for treatment. In 55 instances the infarction was judged to be older than 72 hours and, therefore, were excluded from this review.

The patients were divided into three groups:

1. Those who received no treatment, 90 cases; 73 of whom survived more than 24 hours.

2. Those receiving Dicumarol, 123; of whom 118 survived more than 24 hours.

3. Those who were given heparin and Dicumarol, 149; of whom 139 survived over 24 hours.

There were 32 deaths over-all in the

*Statistical analyses were done by Miss Geraldine Fellers and Dr. Martin Brumbaugh of Bristol Laboratories, Inc., Syracuse, New York.

first 24 hours and only 7 and 2 deaths in the second and third 24-hour periods. The first day's deaths were not considered as alterable by anticoagulants since most died in shock or acute congestive failure. They were, therefore, excluded. The mortality rates and incidences of hemorrhage and thromboembolism are shown in Table 1. When the deaths during the first day are excluded the differences in mortality rates between groups are not statistically significant, though slightly higher in the untreated group and in the group receiving both heparin and Dicumarol. There appears to be no indication that early heparin improved the prognosis of these patients.

TABLE 1.—OUTCOME OF MYOCARDIAL INFARCTION WITH DIFFERENT TREATMENTS

	Treatment Groups	*Deaths*	*Thromboembolism*	*Hemorrhages*
24-hr. Deaths Included	Untreated (90 cases)	42.2%	11.1%	1.1%
	Dicumarol (123 cases)	19.5%	3.3%	5.7%
	Heparin & Dicumarol (149 cases)	26.2%	3.4%	8.7%
24-hr. Deaths Excluded	Untreated (73 cases)	28.8%	13.6%	1.4%
	Dicumarol (118 cases)	16.1%	3.4%	5.9%
	Heparin & Dicumarol (139 cases)	20.9%	3.6%	9.4%

As might be expected, the incidence of clinically recognized thromboembolism was four times as frequent (13.6%) in the untreated group as in the Dicumarol group (3.4%). The early administration of heparin with Dicumarol did not further lower the frequency of that complication. The complication of hemorrhage other than microscopic hematuria was four times more frequent in the Dicumarol group than in untreated cases. With the early addition of heparin, hemorrhage was seven times as frequent as in untreated cases. Of the 20 patients with significant hemorrhage, 5 died. One of these had hemopericardium without apparent cardiac rupture plus cerebral hemorrhage, and one had cardiac rupture. Two cases had sudden deaths but no necropsy was obtained, and one definitely was unrelated to the hemorrhage. Five of the 18 cases with thromboembolism died and that complication definitely contributed to death in 4 of these.

Discussion. The use of death and complication rates for the proper evaluation of therapy in myocardial infarction requires that groups of cases being compared are similar and truly comparable. The comparability of our three case groups was estimated in several ways as shown in Table 2. The mean ages are similar. There was a slightly larger number of females in the group given heparin plus Dicumarol. The severity of the infarction was estimated by two methods in each group. First a modification* of the Russek method[8,9] of designating cases

*A "poor risk" was one exhibiting any of the following upon admission: previous myocardial infarction, intractable pain, extreme or persistent shock, significant cardiac enlargement, gallop rhythm, congestive failure, significant arrhythmias, diabetes, marked obesity, previous pulmonary embolism or thrombophlebitis, varicose veins, hypertension, or angina pectoris.

as "good" or "poor risks" was applied, and all cases so classified according to clinical data available at the time of hospital admission. The proportion of such "poor risks" in our three case groups is shown in Table 2, and is highest in the untreated group. There is no statistical difference of significance between the numbers of poor risks in the three groups however.

A second method used to compare the severity of diseases in the three groups was the "pathologic index rating." This is a scheme of numerical scoring of clinical findings arbitrarily assumed to adversely affect prognosis in myocardial infarction devised by Schnur[10]†. A low total point score indicates a "mild" case and a high one a "severe" case. In Schnur's cases as well

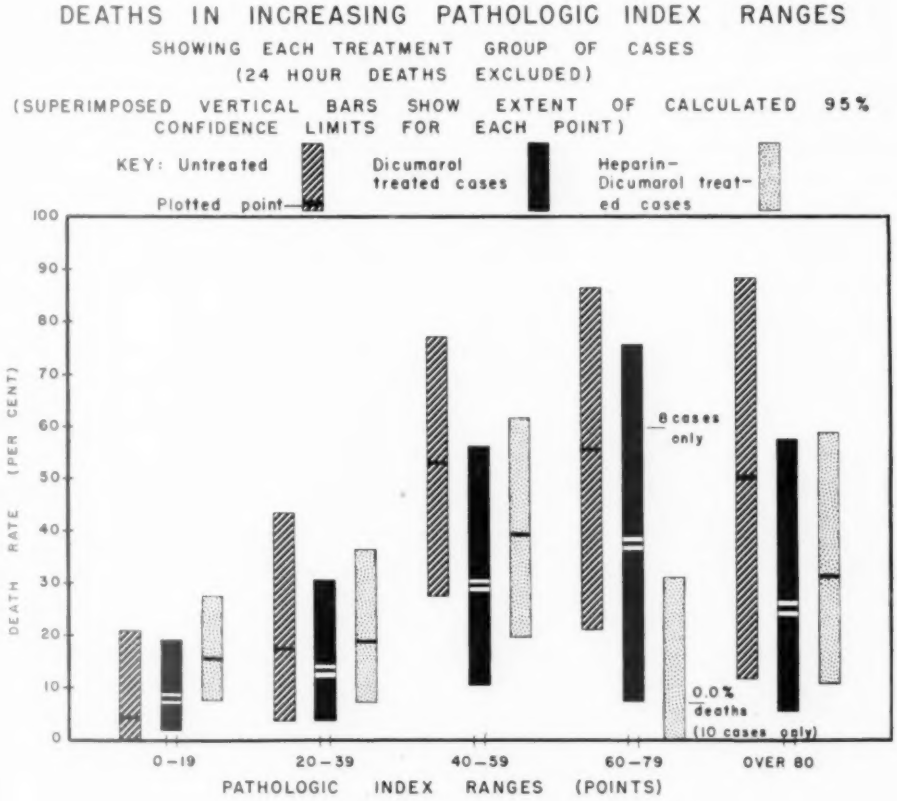

Fig. 1.

†Scoring criteria of admission findings are as follows:

Shock	40 points	Emphysema	10 points
Congestive failure	20–25 "	Cerebral thrombosis	10–25 "
Serious arrhythmias	10–40 "	Hypertension	10 "
Gallop rhythm	15 "	Cardiac enlargement	15 "
Diabetes	10–25 "	Angina	10–30 "
Uremia	10–25 "	Congestive failure	20–30 "
GU infections	10 "	Prev. coronary occlusion	20–30 "

as ours, mortality rate increased with rising "pathologic index ratings." The means of these ratings for our three groups are shown in Table 2, and it is highest in the untreated group. The differences do not, however, reach statistical significance.

Death rates are graphed with increasing "pathologic index ratings" for each group separately in Fig. 1. The calculated 95% confidence limit for each plotted point is shown by vertical bars above and below it. This graph supports the obvious suggestion by Russek[9] that "mild" cases have lower death rates, and "severely" ill ones have higher death rates. There is obviously overlapping of confidence limits between treatment groups, however, for the entire range of severity of illness. Numbers of cases used for each plotting are small but this overlapping prevents our concluding that the use of anticoagulants is more effective in either mild or severe cases.

Neither the "pathologic index" rating scheme nor the determination of "good" or "poor risk" type are perfect determinants of severity of myocardial infarction, but are the only objective schemes available. The clinical factors upon which they are based are arbitrarily presumed to affect adversely the outcome of myocardial infarction. However, there is disagreement upon the prognostic value of many such corollary factors except for some obviously ominous findings such as severe shock, ventricular arrhythmias or acute pulmonary edema. A few examples of such disagreements in the medical literature are listed in Table 3.

In order to evaluate the importance of single clinical features on the mortality rate in myocardial infarction the cases with factors alleged to indicate a poor prognosis in the 417 cases have been compared to the cases who are free of these factors. In order to have statistical significance in a difference in mortality rate of 20% between cases with no adverse clinical features and those with a single adverse clinical feature the numbers of cases required have been estimated in Table 4. Obviously a greater number of cases would be required to show a smaller difference in mortality rate. None of the reports reviewed contain series of nearly such large numbers. It is, therefore, probable that the disagreement on whether a factor such as angina pectoris is ominous or not stems from the analysis of too few cases. If there is this degree of uncertainty of the effect of such accessory clinical findings upon the outcome of myocardial infarction, then prognosis cannot reliably be based upon them. With the multiplicity of such findings usually present and the debatable effect of many of them, accurate prediction of the outcome of a single case is not feasible. This is especially true during the first hours of hospitalization. Nevertheless, the application of schemes such as those of Schnur or Russek to compare large groups of cases retrospectively, is justifiable.

Certainly the addition of heparin to anticoagulant therapy produced no improvement in mortality rate and led to an increased incidence of hemorrhage (9.4%) which approached that of thromboembolic complications in the untreated patients. In fact almost as many patients died with associated significant hemorrhage as those with thromboembolism. Another change in management of this disease over the period of study which may play an important role is the increased activity permitted the patient in bed. This alone may play as important a role in the slight change in mortality rate as anticoagulants, though we have no data to support such an assumption except that the majority of the un-

TABLE 2.—COMPARISON OF CASE GROUPS OF ACUTE MYOCARDIAL INFARCTION

After Deletion of 24 hr. Deaths	*Mean Age*	*Males*	*Females*	*Incidence of "Poor Risks"*	*Average Pathologic Index Rating*
73 untreated cases	59.0 yrs.	71.9%	28.1%	89.1%	37.1 points
118 Dicumarol cases	59.6	73.7	26.3	82.2	29.8
139 heparin and Dicumarol cases	58.1	58.9	40.1	83.5	32.2

TABLE 3.—DIFFERENCES OF OPINION ON EFFECT OF VARIOUS FACTORS IN ACUTE MYOCARDIAL INFARCTION

Factor	*Authors Noting no Adverse Effect on Mortality in Myocardial Infarction*	*Authors Noting Adverse Effect on Mortality in Myocardial Infarction*
Increased age	Russek *et al.*[9] Schnur[11]	Wright, Marple and Beck[15] Doscher and Poindexter[1] Rosenbaum and Levine[7] White and Bland[14] Levine and Brown[3]
Sex: female	Wright, Marple and Beck[15] White and Bland[14] Levine and Brown[3]	Mintz and Katz[6] Doscher and Poindexter[1] Smith *et al.*[13] Rosenbaum and Levine[7]
Obesity	Smith *et al.*[13]	Russek *et al.*[8,9] Wright, Marple and Beck[15]
Diabetes	Smith *et al.*[13] Feldman *et al.*[2] Doscher and Poindexter[1]	Wright, Marple and Beck[15] Master, Dack and Jaffe[5] Mintz and Katz[6]
Previous angina pectoris	Wright *et al.*[15] Mintz and Katz[6] Feldman *et al.*[2] Smith *et al.*[13] White and Bland[14]	Doscher and Poindexter[1]
Previous myocardial infarction	Feldman *et al.*[2]	Wright, Marple and Beck[15] Russek *et al.*[8,9] Doscher and Poindexter[1] Smith *et al.*[13]
Hypertension	White and Bland[14] Mintz and Katz[6] Sigler[12] Smith *et al.*[13] Feldman *et al.*[2] Levine and Brown[3] Master, Dack and Jaffe[5]	Doscher and Poindexter[1] Rosenbaum and Levine[7] Wright, Marple and Beck[15]

treated cases were in the earlier years of the study and the nurses at that time were more rigid about activity. The relatively unimpressive changes in over-all mortality rate with either type of anticoagulant therapy suggests that the "arm chair treatment" may be as satisfactory (Levine and Lown[4]).

Conclusions. Superficial examination of the death rates in these cases suggests that Dicumarol decreases mortality and that the early use of heparin results in more deaths than if Dicumarol were used alone. However, closer examination of the cases studied prevents us from accepting this conclusion. First, there was a significant difference between death rates in treated and untreated cases only if early deaths (24-hour) were counted. If they were omitted the significance disappeared. That the case groups are comparable as to severity of illness is doubtful. The untreated cases were probably more severely ill since their mean "pathologic index rating," as well as the number of "poor risks" was higher than in either treatment group. The changes in death rates in these cases could in this series be due to a difference in severity of illness as well as a difference in treatment. Consequently, no definite conclusions on the apparent benefit of Dicumarol can be drawn. There is in our cases a significantly lower incidence of thromboembolism in treated case groups. It will be noted, however, that the incidence of hemorrhages is high in Dicumarol-treated cases and still higher when heparin is added. No discernible benefit was seen from early heparin administration in conjunction with Dicumarol.

TABLE 4.—APPROXIMATE NUMBERS OF PATIENTS NEEDED IN ORDER TO OBTAIN SAMPLES SUFFICIENT TO SHOW SIGNIFICANCE OF DIFFERENCES BETWEEN DEATH RATES OF "GOOD RISK" PATIENTS AND PATIENTS WITH A SINGLE "POOR PROGNOSTIC" FACTOR

	Number of Cases Needed for a Death Rate Difference of:		
Single Poor Prognostic Factor	*10%*	*20%*	*40%*
Failure on admission	33,600	10,500	3,700
History of thrombophlebitis	33,600	10,500	3,700
Shock	33,600	10,500	3,700
Gallop rhythm	16,800	5,200	1,800
Significant arrhythmia	16,800	5,200	1,800
Intractable pain on admission	11,200	3,500	1,200
Previous infarct	11,200	3,500	1,200
Varicose veins	11,200	3,500	1,200
Diabetes	5,500	1,700	620
Cardiomegaly	3,300	1,050	370
History of hypertension	3,300	1,050	370
Obesity	1,900	610	220
History of angina	1,400	450	160

Summary. 1) The experiences with anticoagulant therapy in acute myocardial infarction in a general hospital from 1947 through 1955 were analyzed in retrospect. Cases were divided into three groups including untreated cases, those given Dicumarol, and those given early heparin plus Dicumarol therapy.

2) The mortality rate was higher in untreated cases but the differences are of no significance unless the early (24-hour) deaths are counted.

3) Cases given early heparin plus

Dicumarol had a higher mortality rate than those given only Dicumarol. The difference, however, is not significant.

4) There was a lower incidence of thromboembolic phenomena in anticoagulant-treated cases compared with those receiving no anticoagulants.

5) Hemorrhagic phenomena occurred in Dicumarol-treated cases four times as often as in untreated cases. In cases given heparin and Dicumarol, hemorrhages were seven times as frequent.

6) Superficial examination of these data, in spite of the lack of statistical confirmation, would suggest that anticoagulants are of benefit. Comparison of the severity of illness in each case group, however, suggests that untreated cases in this series were more seriously ill, and differences in death rates may conceivably be due to that factor.

7) The apparent increase in hemorrhages and the lack of significant alterations in either mortality or incidence of thromboembolism among cases which had early addition of heparin to anticoagulant therapy make its use seem unprofitable.

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(Interlingua on page 674)

TWO CASES OF ATRIAL FIBRILLATION OF MANY YEARS' DURATION REGULARIZED BY QUINIDINE

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Although atrial fibrillation is generally associated with some form of heart disease, it is now well known that this arrhythmia can occur in a transient or permanent form in patients without any other evidence of disease of the heart or any other important organ of the body. This makes up the group of so-called "normal fibrillators" and constitutes about 5% of all cases of atrial fibrillation. In other words, this is not an uncommon condition. It has also been reported that occasionally it may be found in more than one member of the same family (Hanson and Rutledge[6], Levy[8], and Wolff[15]).

The purpose of this communication is to report two instances of atrial fibrillation without other evidence of heart disease of many years' duration occurring in two brothers who were successfully treated by very large doses of quinidine. The son of one of these, aged 8 years, has recently also developed atrial fibrillation and has shown no other evidence of heart disease.

Case Reports: case 1. A.C., P.B.B.H. #9B476: The patient was a 36-year-old South American executive. His chief complaints were palpitation of the heart and pain in the back and left leg. He believed that his heart had been beating irregularly all his life and that "he was born with it." He entered the Peter Bent Brigham Hospital on 5 October 1951. For the previous 17 years the cardiac arrhythmia was identified to be due to atrial fibrillation by annual physical examinations including electrocardiograms. He felt quite well all these years though he had a mild chronic cough occasionally productive of phlegm and had some wheezing in childhood. There was some slight dyspnea on effort in recent months. About 2 weeks before admission he fainted on getting up at night to urinate and was thought to be unconscious for about 20 minutes. He had no similar spells before or since. There was no history of rheumatic fever and no chest pain on effort. Roentgenogram showed a duodenal ulcer several years ago. At the age of 20, he had a luetic infection which was treated with arsenic and bismuth for one year. He had several episodes of gonorrhea.

Family History. He was married, had two healthy children, his father died at 60 and his mother at 30, of influenza. He had 10 brothers and sisters, all well with the exception of one brother (Case #2), who had a problem similar to his own. Four sisters had asthma in their childhood. One of his 2 children, a boy 8 years old, recently developed atrial fibrillation and shows no other evidence of heart disease.

Physical Examination. He seemed quite well. There was no evidence of thyrotoxicosis and the heart was not enlarged. No murmurs were heard but the rhythm was grossly irregular. Apical rate 66. Blood pressure 105/65. The lungs were clear. Abdomen was negative. The thyroid was not palpable. No tremor of his fingers was present. There was no pitting. Peripheral pulses were normal. There were certain neurological findings pointing to a ruptured intervertebral disc in the region of L4 and L5.

Laboratory Data. Hinton test of blood and

cerebrospinal fluid was negative. Urine was negative. All blood counts were normal except for an eosinophilia of 8%. Blood urea nitrogen 10 mg. per 100 ml. Blood proteins 6.3 gm. Blood sugar 74 mg. per 100 ml. Stool examination was negative; basal metabolic rate was minus 12%. Electrocardiogram was normal except for atrial fibrillation; roentgenogram of the heart was normal; gallbladder roentgenogram was normal. Barium enema was negative; upper gastrointestinal roentgenogram was negative except for minimal deformity of the duodenal cap.

Clinical Course. Patient was regarded as having persistent atrial fibrillation of at least 17 years' duration without organic heart disease. He also had a ruptured intervertebral disc. It was decided not to administer digitalis as his cardiac status seemed excellent. He was first given 0.9 gm. of Pronestyl intravenously over a 20-minute period without altering the arrhythmia. The next day he was started on quinidine sulphate therapy. The doses were 0.2, 0.3, 0.4, 0.5 gm. at 4-hour intervals, at 8:00 A.M., 12:00 Noon, 4:00 P.M. and 8:00 P.M. The heart was examined before each dose. On the second and third day each dose was constantly increased until on the third day a single dose of 1.5 gm. was reached. At this point the electrocardiogram showed left bundle branch block and he complained of tinnitus and blurred vision. These symptoms disappeared in the following few hours though the heart was still irregular. The next morning (17 hours after the last dose of quinidine) normal sinus rhythm, without bundle branch block, was present and confirmed by electrocardiogram (Fig. 1).

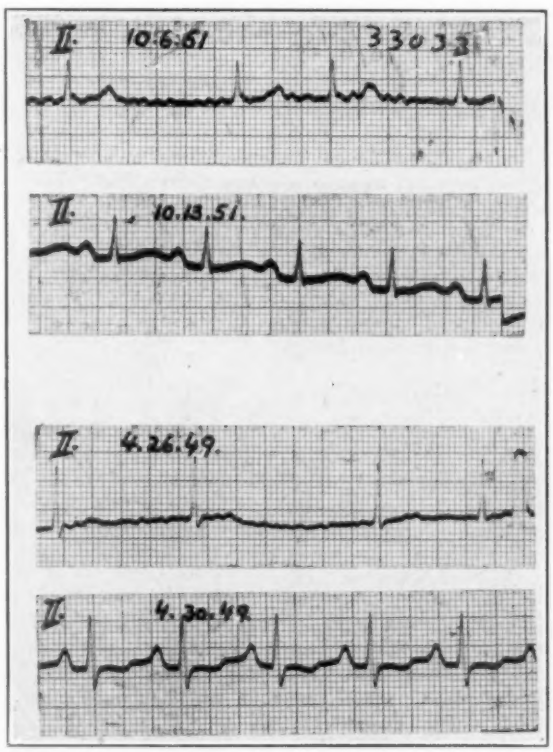

Fig. 1.—Upper two tracings are from Case 1. They show atrial fibrillation on 6 October 1951 and normal sinus rhythm on 13 October 1951, the morning after reversion following quinidine. The lower two tracings are from Case 2. They show atrial fibrillation on 26 April 1949 and normal sinus rhythm on 30 April 1949, the morning after reversion following quinidine.

During the following few weeks 0.2 gm. of quinidine was given four times a day and then completely omitted. Eight days after reversion to a normal sinus rhythm a ruptured intervertebral disc was removed between L4 and L5. The patient made a splendid recovery in every way and has been quite well ever since. The follow-up examination on 12 May 1954 showed a normal sinus rhythm and occasional premature supraventricular beats.

CASE 2. F.C., P.B.B.H. #6A211: The patient was a 37-year-old South American executive, a brother of Case 1, who was first in this hospital from 16 June 1947 to 27 June 1947.

He had been in fairly good health carrying on his duties but complained of vague pain in the region of the apex of the heart and in the right chest. This was not related to effort or food. He was somewhat troubled with palpitation of the heart during the previous 3 years. There was little if any dyspnea on effort; there was no past history of rheumatic fever or allergic manifestations. He had malaria at the age of 13 and gonorrhea at the age of 30. He was married and had 2 healthy children.

Physical Examination. He appeared quite well; blood pressure 120/85; heart was not enlarged, showed no murmurs although the rhythm was grossly irregular, with an apex of 84. Lungs were clear. Abdomen was negative. Peripheral pulses were normal. Thyroid was not felt. There was no tremor of the fingers.

Laboratory Data. Electrocardiogram was typical of atrial fibrillation but otherwise was not remarkable. Blood Hinton was negative. Urine was negative. Blood counts were normal except for 16% eosinophilia. Blood urea nitrogen was 12 mg. per 100 ml.; total protein 7.0. Blood sugar was 107 mg. per 100 ml.; stool was negative. Roentgenogram showed the heart to be very slightly enlarged, 15% above average; left atrium was not dilated. Vital capacity was 3,500 ml. Venous pressure was 70 mm. water; gastrointestinal roentgenogram was normal. Roentgenogram of the gallbladder was normal; basal metabolism rate was plus 37% on first examination and later plus 11%. Protein-bound iodine was 4.3 μg. per 100 ml. (normal).

Clinical Course. The patient was regarded as having atrial fibrillation without organic heart disease. The arrhythmia had lasted at least 5 years. He was kept on a maintenance digitalis dose. He was also given Dicumarol during these days of treatment. Quinidine was instituted four times daily at 4-hour intervals, beginning with a dose of 0.1 gm. The amount of the drug was increased by 0.1 gm. with each dose as mentioned in the previous case. The heart was examined each time before medication was given. After 6 days of treatment atrial fibrillation persisted although a single dose of as much as 2 gm. had been reached. Further quinidine therapy was, therefore, abandoned. He was advised to continue his ordinary duties and maintained on 0.1 mg. Digitoxin daily.

During the subsequent 2 years his condition remained unchanged but he became increasingly worried and fearsome about his heart. He had many episodes of sudden dizzy spells associated with palpitation. He became afraid that he was going to die. He also had spells of sharp precordial pain lasting a few minutes without radiation that were not related to effort. He was readmitted to the Peter Bent Brigham Hospital on 25 April 1949. Physical examination was unchanged. The blood pressure was 120/78. The heart rhythm was grossly irregular as before. The vital capacity was 3,500 ml.; circulation time was 17 seconds and the venous pressure was 120 mm. The electrocardiogram was not remarkable except for atrial fibrillation. The roentgenogram of the heart was within normal limits and on measurement only 3% above normal size. The basal metabolic rate was plus 30% at first and a few days later plus 18%. Radioactive iodine uptake test was normal.

It was decided to try quinidine therapy again. He was continued on digitalis and given Dicumarol. Quinidine sulfate was then administered beginning with 0.2 gm. and increased by 0.1 gm. with each dose at 4-hour intervals four times daily. In several days a single dose of 2.0 gm. was reached. Several hours after this last large dose the heart returned to normal sinus rhythm (Fig. 1). There were no untoward reactions clinically or electrocardiographically to this massive dose of quinidine. He was maintained on 0.2 gm. quinidine three times daily for 2 weeks and then 0.2 gm. only twice daily for the following 2 weeks after which time the quinidine was omitted entirely.

During the following 3 years the heart remained regular and the patient felt quite well, though he was taking no cardiac medication. Atrial fibrillation then returned in 1953. He was given a further trial on quinidine therapy by his home physician in Caracas but without success. Quinidine was stopped

when a dose of 0.8 gm. was reached because the electrocardiogram showed marked abnormalities consisting of a spread of the QRS complexes and frequent brief runs of paroxysmal ventricular tachycardia. Since then the arrhythmia has persisted and he has begun to show the same symptoms he had before, namely, palpitation, dizziness and apprehension.

He was readmitted to the Peter Bent Brigham Hospital 12 September 1956. He appeared well but a little introspective; heart showed no murmurs; it was grossly irregular though not rapid. There was no evidence of congestion. Circulation time was 16 seconds. Vital capacity 3,000 ml. On roentgenographic examination the cardiac contour was not remarkable. While under our care it was decided to try him again on quinidine therapy. He was given 1 mg. of digoxin on the first day and 1.5 mg. on the second day. Treatment was started with 0.4, then 0.6, 0.8 gm. of quinidine sulphate, at 4-hour intervals the first day. He was examined before each dose was administered. On the second day 1.0 gm. and four hours later 1.5 gm. were given. The beat remained irregular and no further quinidine was given because after the last dose the electrocardiogram again showed the threatening arrhythmia (Fig. 2). Also he felt somewhat sickish but the following day his former state returned. He was discharged on a maintenance dose of 0.25 mg. digoxin daily. This trial proved to be unsuccessful as it seemed dangerous to continue large doses of quinidine in the face of ventricular tachycardia and delayed intraventricular conduction which are generally regarded as toxic manifestations of quinidine.

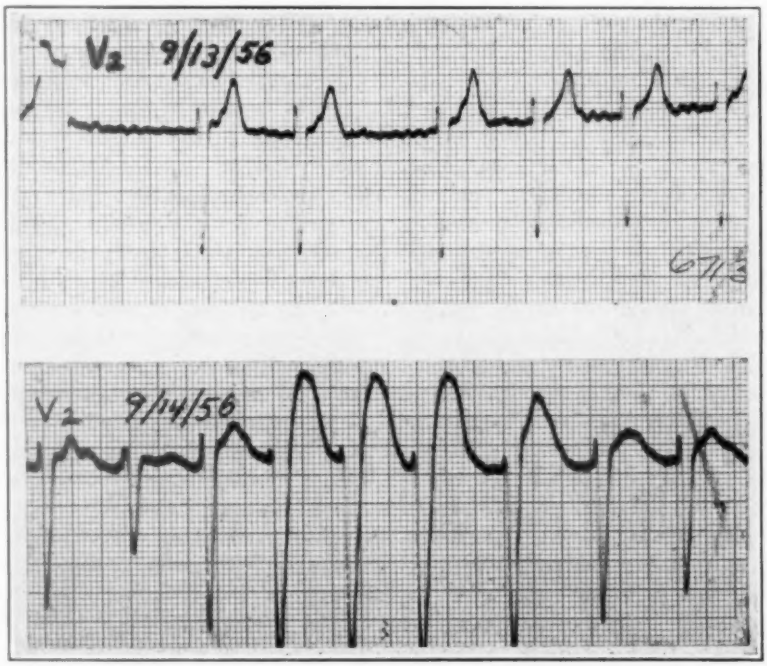

Fig. 2.—Upper tracing Case 2, before quinidine, shows atrial fibrillation on 13 September 1956. Lower tracing 14 September 1956, about 2 hours after a single dose of 1.5 gm. quinidine was given, shows distorted ventricular complexes and brief runs of possible ventricular tachycardia, atrial fibrillation persisting.

Discussion. It has been estimated that in about 6% of all patients exhibiting atrial fibrillation no structural heart disease can be detected by present day clinical means (Friedlander

and Levine[4], Hanson and Rutledge[6], and Orgain, Wolff and White[10]). A most diverse multitude of influences has been incriminated by the patients (and their physicians) as responsible for the onset of atrial fibrillation, in its transient or permanent form, in these otherwise healthy persons. They include physical exertion, gastrointestinal disturbances, upper respiratory infections, alcohol, tobacco, minor traumas, emotional upsets, and others (Phillips and Levine[12], and Sprague[13]).

Anatomo-pathological studies comparing the hearts of nonfibrillators with those of fibrillators have failed to reveal any lesion characteristic of atrial fibrillation (Frothingham[5], and Yater[16]). This diversity of precipitating factors, together with the absence of any specific structural substratum characterizing atrial fibrillation, leads to the assumption that atrial fibrillation is essentially a functional disturbance. The underlying mechanism could be the result of a trigger phenomenon of neurogenic origin in certain individuals who are susceptible to functional nervous instability but are otherwise normal (Phillips and Levine[12]). In this respect it is of interest that this type of arrhythmia is thought by some to be of more frequent occurrence in emotionally labile persons (Hanson and Rutledge[6], and Master and Eichert[9]) suffering from what is described as nervous indigestion, anxiety, fatigue, nervous exhaustion, and the like. Our Case 2 fits well into this category. On the other hand, it is significant that males greatly predominate over females with this condition in the ratio of 10 to one (Friedlander and Levine[4]). One would think that emotional factors would be more prevalent in the female sex.

This condition has a familial tendency on occasion. Atrial fibrillation in otherwise normal hearts in 2 brothers has been reported by Levy[8]. Hanson and Rutledge[6] reported a case of a 79-year-old patient with a normal heart who had had atrial fibrillation for 44 years. The patient's father and a brother were supposed to have had atrial fibrillation for a lifetime and died at the age of 82 and 87 respectively. The same authors reported an additional instance of atrial fibrillation in 2 brothers who both had enjoyed an active and unrestricted existence well into the fifth decade of life without any evidence of heart disease. Wolff[15] reported the occurrence of atrial fibrillation without structural heart disease in 2 pairs of brothers. The present report of this disturbance occurring in 2 brothers and the son of one of them is further evidence of a familial factor in this disturbance.

A fair number of patients exhibiting this type of arrhythmia may be completely unaware of it and its presence may be only incidentally discovered. The most common complaints, in order of frequency, are: palpitation, weakness, breathlessness and syncope (Phillips and Levine[12]). They may cause a significant degree of incapacitation (Master and Eichert[9]). This is exemplified by our second patient.

The prognosis in this group of normal fibrillators in general is considered to be good (Evans and Swann[2], Hanson and Rutledge[6], and Hind and Trier[7]), and the striking feature is the absence of either heart failure or any other important cardiac disability except palpitation in most of the patients (Hanson and Rutledge[6]).

What, therefore, is the justification for instituting a rather heroic course of quinidine therapy in order to achieve reversion to normal sinus rhythm? In certain individuals the therapy becomes imperative because the mere presence of palpitation is troublesome enough to cause incapacitation despite the fact

that the circulatory dynamics are essentially normal. What is more important, and this has not been always sufficiently appreciated, is that such patients occasionally develop congestive heart failure and that all evidence of heart disease may disappear with a complete return to a normal state if the irregularity can be reverted to normal sinus rhythm before irreversible changes have occurred (Brill[1], and Phillips and Levine[12]). There exists, therefore, a small but definite group of patients with moderate to advanced heart failure in whom the entire disability is curable by regularization of the rhythm. Furthermore, Phillips and Levine[12] have suggested that some cases of irreversible heart failure with atrial fibrillation may have started out with atrial fibrillation in an otherwise normal heart, which then, because of prolonged atrial fibrillation, developed cardiac enlargement and heart failure. Such patients over 40 and 50 years of age might well show some evidence of arteriosclerosis of the type seen with advancing years and be loosely classified as having arteriosclerotic heart disease, chronic myocarditis or nonvalvular heart disease. Because they are fibrillators and show evidence of heart failure, and have no hypertension, valvular disease or coronary disease, they are given this noncommittal diagnosis. It is quite likely that some of these cases really started without any organic disease, developed atrial fibrillation and then progressed to irreversible heart failure with cardiac enlargement. If this is true, the entire disability might have been prevented or at least deferred if normal sinus rhythm had been restored by quinidine in the earlier stage of the arrhythmia.

When reversion to normal sinus rhythm is obtained in these cases the regular rhythm is likely to be maintained either indefinitely or at least for a sufficiently long time (a year or more) to have made the therapy worthwhile. This is in contrast to cases with mitral stenosis in which, once the heart has become regularized, fibrillation so often recurs within a few days or weeks.

Very large doses of quinidine were necessary in both cases reported here in order to achieve reversion to normal sinus rhythm. This is, however, not the usual occurrence. Frequently only small doses of quinidine are sufficient to achieve restoration of normal sinus rhythm in this group of "normal fibrillators" (Phillips and Levine[12]). The dose that will be required is, however, entirely unpredictable. It has been shown[12] that the previous duration of the arrhythmia had no influence on the ease with which normal sinus rhythm could be restored or on the dose of quinidine required.

Reversion by quinidine should be undertaken only in a hospital where electrocardiograms can be readily obtained and changes in the mechanism of the heart beat be promptly recognized. The following is a routine procedure adhered to in this hospital:

Digitalis in full doses is administered to all patients with rapid ventricular rates. During recent years anticoagulant therapy (Dicumarol or heparin) has been given in some of the cases while the plan of cardiac treatment was going on. It is not clear from the limited experience whether this has any advantage. It so happens that no embolic or other disastrous complications have developed during quinidine therapy in a fairly large group of such normal fibrillators before anticoagulant therapy was in vogue (Phillips and Levine[12]). It is not unlikely that emboli may occur in this group of patients but it must be a rare event. Initially an oral test dose of 0.2 gm. quinidine is given and, if well tolerated, this is

followed at 4-hour intervals four times daily by additional doses, increasing the amount by 0.1 gm. or 0.2 gm. with each dose. Therefore, 0.2 gm. followed by doses of 0.3, 0.4, 0.5 or by doses of 0.4, 0.6, 0.8, and continuing in this manner at 4-hour intervals are given until reversion to normal sinus rhythm occurs. If reversion occurs, the drug is decreased to a maintenance dose of 0.2 or 0.3 gm. twice a day or three times a day. During the active quinidine therapy the drug should be stopped immediately if the blood pressure falls 20 mm., or more, if the QRS complex widens by 50% or more, if the heart rate rises greatly, or respiratory difficulty, syncope or blurred vision develop. Tinnitus or diarrhea need not prevent continuation of treatment. In general, if the patient looks poorly, treatment should be discontinued.

At the beginning of the treatment when increasing doses of quinidine are given, the ventricular rate often becomes more rapid while the rate of atrial impulse formation becomes slower. This acceleration of the ventricular rate may be uncomfortable to the patient. It should not be permitted to last too long. If reversion to normal sinus rhythm does not occur within a few days, quinidine therapy should be stopped entirely. Quinidine should certainly not be given in small doses over any length of time in persistent atrial fibrillation. It does not achieve regularization and will make it only more difficult for digitalis to slow the heart rate.

As a group, a high percentage of normal fibrillators respond to quinidine therapy and revert to normal sinus rhythm. This is in strict contrast to the results obtained in the treatment of atrial fibrillation in mitral stenosis where regularization does not succeed in more than 1/3 to 1/2 of the cases (Friedlander and Levine[4], and Phillips and Levine[12]). Furthermore, when regularization does occur in normal fibrillators, a normal sinus rhythm is likely to be maintained for a much longer period of time than is the case in mitral stenosis.

Both patients reported here suffered no untoward effects from quinidine therapy despite the large doses employed. This is in keeping with the reported observation that serious reactions to quinidine therapy are very uncommon in this type of patient and it is, therefore, regarded as a safe procedure (Phillips and Levine[12]). This is again in contrast with atrial fibrillation in diseased hearts where quinidine therapy results in the occasional occurrence of embolization. There was no instance of embolism when quinidine therapy was used for reversion in 47 cases of normal fibrillators reported by Phillips and Levine[12]. It would appear that mural thrombi are more likely to occur when organic disease is already present, particularly if the endocardium is involved, if the atria are distended and possibly under increased pressure. Stagnation of blood in the cavity might also be a contributing factor. None of these factors is apt to be present in these so-called "normal fibrillators."

When a patient with atrial fibrillation is found to have no other evidence of heart disease, and other possible causes such as hyperthyroidism can be excluded, reversion to normal sinus rhythm should be attempted by the use of quinidine. It is a safe procedure when carried out under proper supervision and the results are generally very gratifying.

Summary. The case histories of 2 brothers with long-standing atrial fibrillation and no other evidence of heart disease have been recorded. In one, the arrhythmia was known to have lasted

for 17 years; in the other, for at least 5 years. In addition, the son of one of the brothers has the same condition. In both cases huge doses of quinidine were necessary and effective in restoring the heart to normal sinus rhythm (the first case receiving increasing amounts up to a single dose of 2.0 gm. and the second case up to 1.5 gm.). In one reversion has been maintained for 5 years, in the other for 3 years.

The merits and desirability of quinidine therapy in this group of normal fibrillators are discussed.

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SUMMARIO IN INTERLINGUA

Regularisation de Fibrillation Atrial Effectuate per Medio de Quinidina in Duo Casos de Multe Annos de Duration

Es presentate le historia del casos de 2 fratres con fibrillation atrial de longe duration e nulle altere indice de morbo cardiac. In le prime, le arrhythmia habeva cognoscitemente durate al minus 17 annos; in le secunde, al minus 5 annos. In plus, le filio de un del duo fratres ha le mesme condition. In ambe casos enorme doses de quinidina esseva requirite pro restaurar le corde a un normal rhythmo sinusal. In le prime caso, le administrationes esseva augmentate usque al dose individual de 2,0 g; in le altere caso, usque a 1,5 g. In un caso, le reversion ha essite mantenite durante 5 annos; in le altere, durante 3 annos.

Es discutite le meritos e le desirabilitate de therapia a quinidina in iste gruppo de structuralmente normal fibrillatores.

THE EFFECT OF AMMONIUM CHLORIDE INDUCED MATERNAL ACIDOSIS ON THE HUMAN FETUS AT TERM: I. pH, HEMOGLOBIN, BLOOD GASES*†

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The human fetus exists *in utero* at a higher hydrogen ion concentration than that of its mother. Little is presently known of the conditions which maintain this unequilibrated steady state. The only experiment of nature in which it is known to be altered is the occurrence of severe fetal hypoxia, with severe depression of fetal pH.

Lowrey *et al.*[21] have suggested recently that the infant of the diabetic mother might also have a lower than normal pH. However, a review of their excellent data demonstrates that 3 of their 4 infants with abnormally low blood pH were born to mothers being given ammonium chloride. Since this drug is a reliable means of inducing metabolic acidosis in otherwise normal individuals, and since no pH data on these 3 mothers are given, this suggests that the drug rather than the diabetes may have produced the fetal pH effect.

It seemed desirable, therefore, to study the effect of ammonium chloride administered to women at term on the pH, gas content and electrolytes of their blood and that of their infants. A parallel study is in progress concerning diabetic mothers and their infants. The present report deals with the pH, gas and hemoglobin findings on normal maternal and newborn controls and normal patients and their newborns under the influence of ammonium chloride.

Material and Methods. Apparently normal patients in the 38th or 39th week of gestation, who were attending the University of Minnesota Prenatal Clinic were requested to take 6 gm. of ammonium chloride a day. The nature of the study was explained to each patient. The ammonium chloride was in the form of enteric coated tablets, and each patient was given one week's supply. A pH determination was done on maternal peripheral vein blood at this time and at weekly intervals thereafter to check for the development of unexpectedly severe metabolic acidosis. Another group of 25 patients in labor was given 4.3 gm. of uncoated ammonium chloride in order to investigate the effects of metabolic acidosis of short duration.

In none of the patients used in this study were efforts made to control the diet or activities in any way.

When the mother was first seen in the prenatal clinic, approximately 7 ml. of blood was drawn without stasis into a syringe from the antecubital vein. The syringe had been previously prepared by greasing the plunger with sterile mineral oil, followed by 0.1 ml.

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†The experimental material formed part of a thesis submitted by R. C. Goodlin to the Graduate School of the University of Minnesota in partial fulfilment of the requirements for a Master's degree in Obstetrics and Gynecology.

of heparin (heparin sodium, 10,000 U.S.P. units per ml.). The needle was left filled with heparin after the air had been expelled from the syringe. No attempt was made to arterialize the venous blood prior to its shedding. After obtaining the blood, any air bubbles were carefully expelled and the needle was capped with a cork and the entire assembly immersed in ice. It was found that specimens kept in ice in this manner underwent insignificant change in their pH over a 4-hour period.

In those cases delivered by cesarean section, the umbilical cord was gently delivered through the uterine incision before any attempt was made to deliver the infant. The umbilical vessels at this time were often dilated when compared with umbilical vessels of infants delivered vaginally. This was thought to indicate that the samples obtained at cesarean section were from umbilical cords showing little or no spasm, and probably represent more nearly true intrauterine conditions.

In vaginal deliveries, samples were obtained from the umbilical vein and artery. By pointing the needle towards the umbilicus, the amount of umbilical artery blood obtainable was limited only by the amount of anticoagulant in the syringe. The same was true, of course, with the vein by pointing the needle toward the placenta.

All deliveries were done under local (usually 1% procaine) anesthesia, whether they were vaginal or cesarean section deliveries. A few outlet forceps are included but there are no difficult forceps deliveries in this series. No oxygen was given during labor in this series of patients.

At times the infants would respire, either before the shoulders were delivered or before both samples of blood could be obtained. In a small number of cases where rapid sampling was not possible, the cord was doubly clamped. It was hardly ever possible to obtain over 2 ml. of blood from the umbilical artery from the clamped segment of cord. There was no difference in the pH values in the control series between the bloods obtained from the clamped cord and those obtained from the pulsating cord. No gas determinations were done on anything but blood from pulsating cords, and every effort was made to obtain the samples before respiration on the part of the infant.

All determinations were done at least in duplicate. The procedures have been described in detail elsewhere[19]. pH was determined in a glass electrode using the Cambridge pH meter. CO_2 and O_2 content were determined on whole blood by the method of Scholander. The 95% confidence interval is $\pm$ 0.6 mM./L. for CO_2 and $\pm$ 0.6 vol.% for O_2 for duplicates. The hemoglobin was determined by spectrophotometry of a dilute solution of whole blood at 414 mμ. The 95% confidence interval is $\pm$ 0.4 gm.% for duplicates.*

In this and previous studies it has been assumed that the oxygen capacity of fetal blood is the same as that of adult blood, that is, 1.34 ml. of oxygen per gm. of hemoglobin. Minkowski has questioned this assumption[36], since he has found widely varying Hüffner coefficients on a group of bloods drawn from human infants at birth.

In order to test this, a group of 26 blood samples from newborns was examined as follows: Hemoglobin concentration was determined as above. An aliquot was equilibrated in a 100 ml. tonometer at 37° C. with gas approximately 95% oxygen and 5% CO_2. Its oxygen capacity was then determined by the Scholander method. The oxygen content of the blood as drawn was measured. Finally, the oxygen saturation was determined by the method of Nahas[24]. In this technique the optical density of 3 laked aliquots of blood, which have been respectively untreated, oxygenated and reduced, is measured at 505 and 605 mμ in a spectrophotometer. The result is, therefore, independent of hemoglobin concentration and of any assumptions as to the oxygen capacity of hemoglobin.

Oxygen saturations based upon oxygen content divided by the hemoglobin content compare reasonably well with the Nahas values. When a Hüffner coefficient was calculated by comparing these pairs of saturation values, a range was found almost as great as that in Minkowski's data, with a slightly higher mean. However, the extremes tend to occur with very high and very low oxygen contents and emphasize the statistical importance of a large denominator in dealing with a ratio. There is no significant deviation

*The pCO_2 values reported here are calculated from the plasma CO_2 content and pH in the Henderson-Hasselbalch relationship. The values in R.C.G.'s thesis were based on a nomogram and, therefore, are slightly different. In the course of the calculations, errors in pH and oxygen saturation values in the thesis were found. These have been corrected in this report. In no case do these corrections alter the conclusions.

of these data, or those of Minkowski, from an assumed oxygen capacity of hemoglobin of 1.34 ml. per gm. if the errors of the methods are considered. Indeed, in Minkowski's data there is no significant difference between his values on adult controls and those in his neonatal series. Although the statistical treatment of differences between means of groups of ratios is extremely complex, a rough estimate suggests that there is no difference between the mean of the present data and that found by Minkowski.

Corresponding values for a group of normal women and their infants at the time of delivery are presented in Tables 2, 3 and 4. The maternal pH and oxygen saturation are essentially unaltered from the antepartal values as a result of normal labor. The maternal plasma CO_2 content and pCO_2 are both reduced, suggesting a mild compensated respiratory alkalosis, probably due to hyperventilation in labor. The fetal values exhibit the lower pH and higher CO_2 content and pCO_2 of the fetus as compared with its mother, as well as a higher hemoglobin. The oxygen content of umbilical vein blood is higher than that of the maternal peripheral (arm) vein although its saturation is lower. The umbilical artery blood is markedly unsaturated, with a corresponding low pH and high pCO_2.

In Fig. 1, the pH of maternal peripheral vein blood is charted as abscissa

TABLE 1.—pH, HEMOGLOBIN CONTENT, PLASMA CO_2 CONTENT AND PRESSURE, OXYGEN CONTENT AND SATURATION IN PERIPHERAL BLOOD OF 26 NORMAL WOMEN IN THE 39TH WEEK OF PREGNANCY:

	pH	*Plasma CO_2 content mM./L.*	*Plasma pCO_2 mm. Hg*	*Oxygen content vol. %*	*Oxygen saturation %*	*Hemoglobin gm. %*
Mean	7.37	21.7	37.2	10.8	70	11.5
Standard deviation	0.02	2.1	3.5	3.1	19	1.2

TABLE 2.—MATERNAL PERIPHERAL VEIN BLOOD IN CONTROL GROUP AT TIME OF DELIVERY

Case No.	*pH*	*Plasma CO_2*	*Plasma pCO_2*	*O_2*	*O_2 Sat.*	*Hgb.*
3	7.35	17.5	31.5	11.2	72	11.7
61*	7.42	21.8	33.1	10.5	72	10.9
85	7.37	22.6	38.4	11.5	73	11.8
86*	7.41	18.4	28.5	13.0	71	13.6
99	7.28	16.5	33.9	10.5	57	13.8
106	7.36	23.6	40.9	5.5	36	11.4
107	7.42	18.3	27.8	——	—	9.8
111	7.36	18.8	32.5	16.3	90	13.6
122	7.37	19.1	32.4	15.8	100+	11.2
128	7.35	24.2	42.9	7.8	53	11.1
X	7.39	20.8	33.6	13.9	81	12.8
Mean	7.37	20.2	34.1	11.6	71	12.0

* Cesarean section

In view of this, oxygen capacity in the present study is calculated from the hemoglobin concentration on the basis of 1.34 ml. per gm., subject to the confidence intervals indicated.

Results. The mean values for pH, plasma CO_2 content and pCO_2 oxygen content, hemoglobin and oxygen saturation in peripheral blood of 26 normally pregnant women at the 39th week of gestation are presented in Table 1. pH determinations alone were done in 61 additional women, the mean pH of the 86 cases being 7.38.

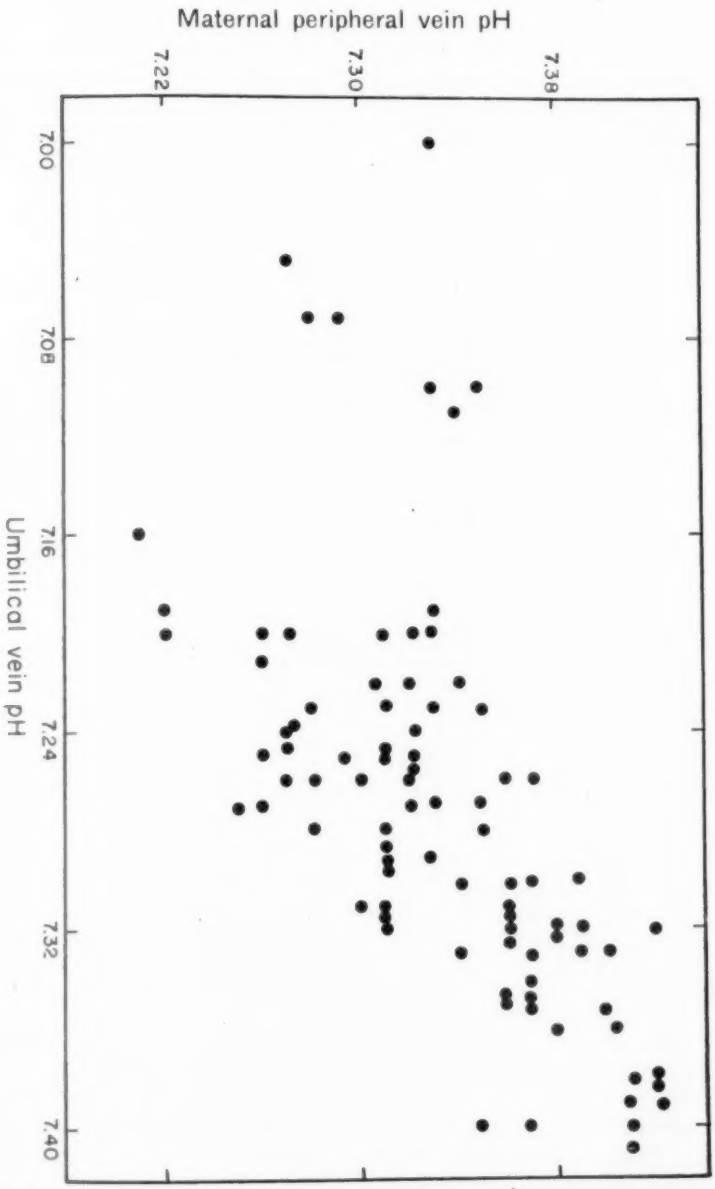

Fig. 1.—Hydrogen ion concentration of umbilical vein blood at the time of delivery plotted against the hydrogen ion concentration of peripheral vein blood of the infant's mother. Normal patients and those receiving ammonium chloride are included.

and of umbilical vein blood in the corresponding fetus as ordinate, for 89 patients and their infants, in both the control and experimental groups. It can be seen that there are only ten instances in which the fetal umbilical vein pH is equal to or greater than maternal. The mean fetal-maternal gradient for the entire group is —0.06 pH units.

One of the patients in the control group, Case 99, and her infant were found to have distinctly lowered pH values. She was clinically unremarkable. Lactic acid concentrations in these bloods were about three times normal although labor was uneventful. There is no satisfactory explanation for this.

The effect of oral administration of 6 gm. enteric coated ammonium chloride a day on blood pH can be seen in Table 5. The striking reduction of pH in both mothers and infants is established within 3 days and remains stable thereafter as long as ingestion of the drug continues. There is no evidence of a cumulation of effect or of any sufficient compensatory mechanism within the 24-day period.

Eleven of these patients were selected for detailed study, on the basis of marked changes in pH. They therefore represent a somewhat more extreme picture than the group as a whole and serve to emphasize the nature of the changes of induced metabolic acidosis. The results are pre-

TABLE 3.—UMBILICAL VEIN BLOOD AT TIME OF DELIVERY IN CONTROLS

Case No.	*pH*	*Plasma CO_2*	*Plasma pCO_2*	*O_2*	*O_2 Sat.*	*Hgb.*
3	7.31	20.0	38.6	16.5	74	16.7
61	7.37	23.6	40.0	15.1	74	15.2
85	7.35	24.7	44.5	13.4	64	15.6
86	7.42	18.6	28.2	12.2	60	15.3
99	7.26	19.1	41.0	15.0	73	15.2
106	7.32	22.4	42.3	14.1	78	13.5
107	7.37	22.4	37.9	12.2	57	15.9
111	7.30	25.0	49.5	8.2	40	15.1
122	7.39	24.2	39.2	13.0	62	15.0
128	7.30	28.0	55.2	7.8	37	15.8
X	7.36	23.5	40.7	12.5	62	15.0
Mean	7.34	22.9	41.6	12.7	62	15.3

TABLE 4.—UMBILICAL ARTERY BLOOD AT TIME OF DELIVERY IN CONTROLS

Case No.	*pH*	*Plasma CO_2*	*Plasma pCO_2*	*O_2*	*O_2 Sat.*	*Hgb.*
3	7.20	23.8	58.0	2.9	13	16.9
61	7.34	22.9	41.3	8.1	41	14.9
85	7.27	28.2	59.3	3.9	18	15.9
86	7.36	22.1	38.2	3.1	16	14.8
99	7.16	22.2	59.1	5.3	27	14.7
106	7.23	26.1	59.9	7.7	41	14.1
107	7.34	26.2	47.4	5.8	27	16.1
111	Insufficient blood.					
122	7.27	26.4	55.6	4.4	23	14.4
128	7.27	29.7	62.5	7.9	37	16.0
X	7.33	26.0	48.1	7.1	35	15.1
Mean	7.28	25.3	52.9	5.6	28	15.3

sented in Tables 6, 7 and 8. In the mothers, the CO_2 content is lower and the pCO_2 higher than in the control group. The hemoglobin and oxygen content and saturation are unaltered.

In the infants born to these acidotic mothers, the blood pH is strikingly reduced, well beyond the range of normal. Concomitantly, the CO_2 content is slightly lowered while the pCO_2 is markedly elevated. With this, there is a considerable decrease in oxygen content and saturation in both the umbilical artery and vein. It must be emphasized that these infants, although in some cases strikingly cyanotic at birth, were otherwise clinically normal, had no difficulty in establishing and maintaining respirations and were healthy in the immediate neonatal period. This is true even of infant 103, with a pH of 6.93 and a pCO_2 of 95.4 in the umbilical artery blood at birth.

TABLE 5.—pH OF MOTHERS TAKING AMMONIUM CHLORIDE AND pH OF INFANTS AND MOTHERS AT TIME OF DELIVERY

	Maximum Days of Ammonium Chloride							
	0	*3*	*6*	*9*	*12*	*15*	*18*	*24*
Mother								
No. of cases	86	7	28	19	27	10	9	9
Average pH	7.38	7.32	7.32	7.31	7.32	7.32	7.32	7.32
Mother at delivery								
No. of cases	28	5	8	16	13	4	7	10
Average pH	7.37	7.30	7.31	7.31	7.32	7.31	7.31	7.32
Umbilical vein								
No. of cases	28	5	7	16	13	3	7	10
Average pH	7.32	7.25	7.20	7.26	7.27	7.23	7.20	7.23
Umbilical artery								
No. of cases	28	5	7	15	12	4	7	10
Average pH	7.28	7.17	7.14	7.19	7.19	7.17	7.12	7.18

TABLE 6.—MATERNAL PERIPHERAL VEIN BLOOD AT TIME OF DELIVERY IN MOTHERS RECEIVING AMMONIUM CHLORIDE

Case No.	*Days on NH_4Cl*	*pH*	*Plasma CO_2*	*Plasma pCO_2*	*O_2*	*O_2 Sat.*	*Hgb.*
2	7	7.21	16.5	39.4	9.9	66	11.2
6	5	7.28	21.7	44.7	9.7	50	14.5
11	8	7.30	19.4	38.3	14.1	76	13.9
20	7	7.26	16.6	35.6	16.2	89	13.6
22	6	7.29	19.2	38.7	12.8	78	12.1
23	10	7.27	14.3	30.1	12.3	69	13.3
46	20	7.27	17.5	36.8	11.3	61	14.1
64	23	7.34	20.0	36.1	12.0	75	12.4
77	12	7.27	16.2	34.2	7.3	43	12.6
98	*	7.22	17.7	41.4	10.0	61	12.3
103†	*	7.33	18.1	33.5	12.7	80	11.8
Mean		7.28	17.9	37.2	11.7	68	12.9

* Uncoated NH_4Cl † Cesarean section

As stated, a small group of mothers received uncoated ammonium chloride just before delivery. The results of pH studies on their peripheral blood, and the bloods of the umbilical cord are presented in Table 9. Maternal pH is seen to drop to the expected extent within a 4-hour period and to remain at about that level for 24 hours. Fetal umbilical blood pH is nevertheless at

about normal levels at 4 hours and does not drop to the expected maternal-fetal gradient until 8 hours after administration of the uncoated ammonium chloride. Although the numbers are small, there is a suggestion that the fetal blood pH first lags behind maternal pH changes, then overshoots to unusually low values and gradually returns to less than a normal gradient. Case 98 in Tables 6, 7 and 8 exemplifies the relationships with a low maternal pH and small gradient and Case 103 in the same tables those with a higher maternal pH and markedly lower fetal pH.

It will be noted in Fig. 1 that 7 infants were studied whose umbilical vein pH was below 7.15 at birth. The details for 6 of these may be found in Tables 7 and 8. All 7 infants were born after uneventful labors and did well.

Seven patients were studied during recovery from ammonium chloride acidosis. They had not been given the drug for from 3 to 5 days. Maternal vein pH was 7.37, umbilical vein pH 7.37 and umbilical artery pH 7.27. This resembles the situation in patients 24 hours after a single dose of uncoated ammonium chloride in that the usual fetal-maternal gradient is decreased.

TABLE 7.—UMBILICAL VEIN BLOOD IN INFANTS BORN TO MOTHERS RECEIVING AMMONIUM CHLORIDE

Case No.	*pH*	*Plasma CO_2*	*Plasma pCO_2*	*O_2*	*O_2 Sat.*	*Hgb.*
2	7.16	18.0	47.8	16.7	71	17.5
6	7.07	20.9	67.2	9.0	37	18.2
11	7.26	23.0	49.4	12.3	59	15.5
20	7.20	20.6	50.3	13.7	60	17.0
22	7.07	23.9	76.9	5.0	26	14.5
23	7.25	18.7	41.0	9.0	39	17.0
46	7.05	15.5	52.0	11.5	63	15.8
64	7.11	25.0	73.8	4.1	20	15.4
77	7.20	16.4	40.2	11.5	57	15.0
98	7.20	23.2	56.8	9.0	46	14.6
103	7.00	21.0	77.9	4.7	21	16.4
Mean	7.14	20.6	57.6	9.7	45	16.1

TABLE 8.—UMBILICAL ARTERY BLOOD IN INFANTS BORN TO MOTHERS RECEIVING AMMONIUM CHLORIDE

Case No.	*pH*	*Plasma CO_2*	*Plasma pCO_2*	*O_2*	*O_2 Sat.*	*Hgb.*
2	7.11	19.8	58.6	4.8	24	15.1
6	Insufficient blood					
11	7.19	25.3	63.2	2.7	13	15.0
20	7.16	22.9	61.0	6.5	29	16.8
22	7.02	23.3	83.1	3.8	20	14.3
23	7.23	21.2	48.6	4.2	20	15.7
46	6.90	17.3	78.6	3.2	15	15.6
64	7.07	25.6	82.2	1.7	8	15.6
77	7.03	19.2	66.9	3.1	16	14.5
98	7.16	25.2	67.0	4.2	21	14.6
103	6.93	22.4	95.4	1.6	7	16.3
Mean	7.08	22.2	70.5	3.6	17	15.4

Discussion. The exact acid-base status of the pregnant woman is as yet undecided. Hasselbalch, in 1912, noted a decrease in the alkali reserve of pregnant women[15]. Oard and Peters, in 1926, agreed that there was a decrease

in the alkali reserve and found it lowered as early as the third month of gestation[27]. While Oard and Peters did no pH studies, they felt that the electrolyte picture in the pregnant woman represented hyperventilation and probably a compensated metabolic acidosis since they found the total base and the alkali reserve were reduced. Williamson, in 1926, decided on the basis of the decreased alkali reserve in pregnant women that they were in a state of uncompensated metabolic acidosis[39]. Myers, Muntwyler and Bill, in 1932, from their studies on alveolar air carbon dioxide, tidal volume, and blood pH, and also from reviewing the literature, suggested that the pregnant woman in the third trimester is in a state of uncompensated alkalosis due to hyperventilation[23]. Dieckmann and Wegner, after extensive investigations, in 1934, agreed that pregnant women had a decrease in the total base, but found the pH, using the colorimetric method, to be normal[5]. To these observers, this electrolyte pattern represented compensated alkalosis. They felt there was no indication of any acidosis of pregnancy. Siedentopf and Eissner, in 1929[34], in 94 cases, using the hydrogen gas electrode, and Eastman, in 1932[7], first found the pH of the term pregnant woman to be normal (7.39). Noguchi working in 1937, using the first micro gas electrode, found the pH to be 7.39 in some 10 cases at term[26].

W. Blair Bell *et al.* appear to be the first to have attempted accurate measurement of the pH of the blood of the human fetus[3]. These authors were considering the placenta as a neoplastic organ and attempted to apply Warburg's chemical proof of malignancy. In the course of their study, they measured the pH of the blood of the umbilical artery and vein, as well as the maternal ovarian and uterine vein and the pH of the amniotic fluid. Their values are low when compared with present day results, perhaps because they made no provision to prevent the formation of lactic acid. Their pH's, the average of 5 cases, determined at 18° C. were: maternal vein 7.31, maternal artery 7.32, umbilical vein 7.15, umbilical artery 7.02. They were, however, the first to appreciate the higher hydrogen ion concentration of the human fetus when compared with its mother.

Siedentopf and Eissner measured the pH of the umbilical vein blood as 7.37 in 94 cases in 1929 using the hydrogen electrode[34]. Haselhorst and Stromberger, in 4 cases of cesarean section, found the fetal vein values to be less than the maternal vein pH in 3 cases[14]. Haselhorst and Stromberger's method

TABLE 9.—MEAN pH OF MATERNAL PERIPHERAL VEIN BLOOD IN 19 PATIENTS GIVEN 4.3 gm. OF UNCOATED AMMONIUM CHLORIDE PRIOR TO DELIVERY, AND THEIR NEWBORNS.

No. of hours NH_4Cl given before delivery	4	8	12	16	24
No. of cases	5	4	3	4	3
Mean maternal pH before medication	7.36	7.37	7.36	7.38	7.36
Mean maternal pH at time of delivery	7.30	7.27	7.29	7.30	7.30
Umbilical vein at time of delivery	7.36	7.18	7.20	7.27	7.28
Umbilical artery at time of delivery	7.30	7.08	7.12	7.18	7.20

of determining the pH was interpolation from the carbon dioxide dissociation curve according to an earlier method of Barcroft. Eastman and Noguchi agreed with Siedentopf and Eissner that the umbilical vein pH was less than the maternal antecubital vein pH. Kaiser, in 1953, in 12 cases found that the average of the maternal vein pH was 7.38, umbilical vein 7.32, umbilical artery 7.26[18]. Kaiser's cases were all cesarean sections done under local anesthesia with the cord sample obtained while the fetus was still *in utero*. Noguchi's and Eastman's cases were vaginal deliveries with one exception. With the exception of Kaiser's data, the maternal blood samples in these studies were from peripheral veins, usually the antecubital. Kaiser found the mean of the peripheral vein pH to be 7.38, the uterine vein 7.36. It then appears from the cited literature that the human fetus *in utero* exists at a higher hydrogen ion concentration than its mother or the normal human.

There have been numerous investigations of blood oxygen and carbon dioxide concentrations in the mammalian fetus (Eastman[7,9], Eastman, Geiling and DeLawder[8], Goldbloom and Gottlieb[11], Greenburger and Holkup[12], Kaiser and Cummings[19], Minkowski[22], Noguchi[25], and Walker[38]). The majority of the human fetal studies have been concerned with asphyxia neonatorum and with the correlation between the clinical status of the infant and the various gas values. The average of the various studies agree fairly well considering the different methods of sampling and determination. The umbilical vein oxygen content is approximately equal to the maternal peripheral vein oxygen content. The carbon dioxide tension is always higher in the umbilical artery than in the maternal peripheral vein (Barron[2], Huggett[17], and Kane and Kreiselman[20]). Romney found the uterine vein oxygen content to be slightly higher than that of the umbilical vein, but his cases were elective cesarean sections done under spinal anesthesia[31]. The umbilical artery oxygen content is usually approximately 7 vol.% less than that of the umbilical vein (Smith[35]). While the carbon dioxide tension has always been found to be higher on the fetal side, the values have varied considerably in the literature (Barron[3], Cross, Killick and Huggett[4], Huggett[17], Kaiser and Cummings[19], and Roos and Romijn[32]).

The significance of the human fetal pH has remained unclarified. Some students of this problem have assumed that it represents an uncompensated metabolic acidosis (Raiha[29], and Siedentopf and Eissner[34].) Young, however, has made the interesting observation that the situation in the rabbit fetus is that of an uncompensated respiratory acidosis[42], and Kaiser and Cummings have reached a similar conclusion for the fetal lamb[19]. To support the concept of a metabolic acidosis of the human fetus relative to its mother, many references have been made to the possibility of anaerobic glycolysis. While there is no direct proof of the fetus's need of anaerobic glycolysis due to insufficient placental oxygen supply, certain observations have made this theory attractive.

1. The oxygen tension in the fetal cell has been estimated to be 16 mm. of mercury (Eastman[6], and Noguchi[25]), indicating a severe degree of hypoxia. This may be an under-estimation as the umbilical artery from which this figure is calculated represents a mixture of both arterial and venous blood.

2. There have been frequent observations of the increased values of fetal blood levels of lactic and pyruvic acid as compared with adults (Bell *et al.*[3], Eastman[6], Himwich *et al.*[16], Raiha[29],

and Wilson *et al.*[40]). These organic acids may be the products of increased anaerobic glycolysis.

3. The fetuses of all animals studied have a greater resistance to hypoxia than adults, and this resistance can be abolished by the inhibition of anaerobic glycolysis (Cross, Killick and Huggett[4], Himwich, Alexander and Fazekas[16], and Romney *et al.*[31]).

Considerable clinical significance has been attached to possible fetal acidosis. Wilson *et al.*, in their study of asphyxia neonatorum found an average fetal vein pH of 7.095, and an oxygen content of 1.995 vol.%[40]. Eastman found a pH of 7.04, and an oxygen of 1.3 vol.%[7]. Both Eastman and Wilson believed that the severe hypoxia is the essential feature of asphyxia neonatorum. Noguchi disagreed, as in his series of infants with asphyxia neonatorum, a high hydrogen ion concentration was the constant finding. Noguchi, however, did believe the hypoxia was probably the initiating event in asphyxia neonatorum[25].

The development of maternal acidosis in a viable diabetic pregnancy has been considered an indication for termination of the pregnancy. The fetal loss found in diabetic pregnancies has been ascribed to the high incidence of maternal acidosis (Pedowitz and Shelien[28]). Acidosis has also been blamed for the high fetal loss frequently found in prolonged labor. As stated, it was the observation of a lowered fetal pH in infants born to diabetic mothers which stimulated the present effort to produce this in otherwise normal mothers and infants.

Ammonium chloride has been used for many years as a diuretic, and as an agent to acidify the urine in urinary tract infections. In the usual therapeutic dose, the incidence of toxicity to ammonium chloride is extremely low. Haldane and Følling were the first to study the acidotic effect of this drug in detail[10,13].

Recently, studies have been made using large doses of ammonium chloride in an effort to investigate the renal mechanisms of combating acidosis. These investigations show a rapid rise of the serum chloride and a decrease of the serum bicarbonate (Sartorius, Roemmelt and Pitts[33]). The urine acidity increases slightly and there is a rise in the urine chloride excretion (Rector, Sheldin and Copenhever[30]). With an ammonium chloride acidosis, the blood pH will frequently drop from an average of 7.40 to 7.28 during the first 3 days of medication (Sartorius, Roemmelt and Pitts[33]). The formation of the ammonia in the kidney tubules in the human during ammonium chloride administration exhibits a certain inertia so that the ammonia formation reaches a maximum intensity after some days, usually 3 to 4, and continues for some time after the cessation of the induced acidosis. After the third or fourth day, with the increase in amount of urinary ammonia, the body stores of sodium and potassium are spared and the urine titrable acid increases. Because the body stores of base are protected by the ammonia production, the ammonium chloride has no further diuretic effect. The pH will usually rise at this time to approximately 7.32 and remain there until the ammonium chloride is discontinued. After the discontinuance of the ammonium chloride, an alkalosis develops, probably from the continued renal production of ammonia. This alkalosis generally reaches its maximum on the fifth day after discontinuing the medication and subsides, the pH being normal on the tenth day (Wood[41]).

Studies on normal and abnormal pregnant women have shown that they react to ammonium chloride in the

same way as the nonpregnant individual (Assali, Herzig and Singh[1]).

The present study has provided information elucidating a number of the problems reviewed above. It must first be stated that the majority of the studies of the blood biochemistry of the pregnant female, including this, have been done on peripheral vein blood, which, because of the altered state of the peripheral venous circulation in pregnancy, is at best a highly variable biochemical material. Reference to the large standard deviations of the pCO_2 and oxygen saturation in Table 1 and the ranges observed in Tables 2 and 6 makes this clear. It can nonetheless be stated that the present data are consistent with the conclusion that in pregnancy there is a mild compensated respiratory alkalosis. Appropriate electrolyte studies of these same patients will be reported later. This alkalosis appears to be increased by normal labor, presumably due to hyperventilation, but nevertheless well within the capacities of the blood buffer systems.

The fetus in the normally pregnant woman maintains a positive hydrogen ion concentration gradient of about −0.06 pH unit. Related to this is the positive pCO_2 gradient. The rare exceptions to these relationships are probably explicable on the basis of the variability of maternal peripheral venous blood.

As a metabolic acidosis is imposed upon the maternal organism, the fetus tends to maintain its unequilibrated relationship and its pH drops. The pCO_2 gradient increases considerably. There is no suggestion that the fetal kidneys (or lung, which may have some excretory activity into amniotic fluid) are active in the regulation of these conditions. If the placenta can be considered both lung and kidney for the fetus, this then resembles an uncompensated respiratory acidosis. Concomitantly, the oxygen saturation falls to very low levels. The newborn infant, however, exhibits little in the way of difficulty. Although a few of the infants in the present experimental group were found to have blood biochemical changes as severe as that previously observed with fatal asphyxia neonatorum, they all did well. The 3 infants in Lowrey's series born to diabetic mothers, who did well despite "acidosis," were all born to women receiving ammonium chloride. This almost certainly demonstrates that it is not the abnormal laboratory findings but their cause, and perhaps the period of time over which that is operative, that makes the difference in clinical outcome. The fetus may withstand an alteration of its blood toward increased pCO_2 and decreased pO_2 when this takes place slowly over a period of hours by deriving more and more of its energy from anaerobic systems. It may not be able to make this conversion in a matter of minutes. On the other hand, the fact that the fetus can withstand biochemical changes out to the extremes of the capacities of its blood buffers must not be a source of false security. Under other than experimental conditions this may create a situation in which an additional insult such as a difficult delivery or a minor obstruction to cord flow is rapidly fatal.

Two limited sets of data are worthy of special note, although they are based on very small groups. When mothers in the present study were pushed into acidosis rapidly by the exhibition of uncoated ammonium chloride, the usual fetal-maternal pH gradient appeared to be reversed during the first few hours. The umbilical vein blood pH remained at essentially normal levels despite a drop in maternal pH. Conversely, in the mothers recovering from ammonium chloride, the pH

gradient diminished to zero, with a relatively high umbilical vein pH. This resembles the small group observed 24 hours after the single dose of uncoated drug except that in the latter both pH values were relatively low. A number of explanations can be hypothesized to explain this, but unfortunately, there are not sufficient data to prove any of them. It is clear, however, that there can be a distinct time lag in the adjustment of pH in the fetus *in utero* to its *milieu extérieur*, which suggests that some component in the system, present ordinarily or only under these special conditions, is relatively non-diffusible. The adjustment to new conditions necessitated by maternal acidosis may persist in the fetus after the acidosis is corrected and may, with the same time lag as a factor, result in over-compensation. In essence, the fetus or placenta is responding to changed conditions with efforts of its own to maintain the steady state.

Summary. Maternal acidosis produced by the exhibition of ammonium chloride to pregnant women at term produces in their fetuses reduced pH, increased pCO_2 and reduced oxygen saturations as measured in umbilical blood. In some cases these changes, disproportionate to those observed in the mothers, are as severe as those previously described with fatal apnea neonatorum following dystocia. All the infants nevertheless did well clinically in the neonatal period.

The data suggest a time lag in the initial adjustment of the fetus to maternal acidosis and an overshooting of adjustment during maternal recovery. The fetus thus appears itself to be adjusting to changed conditions in its *milieu extérieur*.

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SUMMARIO IN INTERLINGUA

Le Effecto Exercite Super le Feto Human al Termino per Acidosis Materne Inducite per Chloruro de Ammonium

Acidosis materne producite per le exhibition de chloruro de ammonium a feminas pregnante al termino effectua in le fetos un reduction de pH, un augmento de pCO_2, e un reduction del saturation oxygenic mesurate in sanguine del cordon umbilical. In certe casos iste alterationes es foras de proportion al alterationes correspondente in le matre e attinge le grados de severitate previemente describite in mortal casos de apnea de neonatos post dystocia. Nonobstante, omne le infantes faceva clinicamente bon progressos durante le periodo neonatal.

Le datos suggere un retardo in le adjustamento initial del feto al acidosis materne e un hyperadjustamento durante le restablimento materne. Assi le feto mesme pare adjustar se a alterate conditiones in su milieu externe.

SUMMARIO IN INTERLINGUA

(See page 647 for original article)

Un Studio Clinic de Anticoagulantes in Acute Infarcimento Myocardial, con Referentias Particular al Uso Immediate de Therapia a Heparina

1. Esseva analysate in retrospecto le experientias colligite ab 1947 usque al fin de 1955 in le uso de therapias anticoagulante con le patientes de acute infarcimento myocardial in un hospital general. Le casos esseva dividite in tres gruppos: (1) illos non tractate, (2) illos tractate con Dicumarol, e (3) illos tractate immediatemente con heparina plus Dicumarol.

2. Le mortalitate esseva plus alte in le non-tractate casos, sed le differentia non es significative si le mortes durante le prime 24 horas es excludite.

3. Le gruppo tractate immediatemente con heparina e Dicumarol habeva un plus alte mortalitate que le gruppo que recipeva solmente Dicumarol. Tamen, le differentia esseva statisticamente non significative.

4. Esseva constatate un plus basse incidentia de phenomenos thromboembolic inter le casos tractate con anticoagulantes in comparation con le casos que recipeva nulle anticoagulantes.

5. Phenomenos hemorrhagic occurreva in casos tractate con Dicumarol quatro vices plus frequentemente que in casos non tractate. In casos tractate con heparina e Dicumarol, phenomenos hemorrhagic esseva septe vices plus frequente que in casos non tractate.

6. Le examine superficial de iste datos pare suggerer, in despecto del absentia de un confirmation statistic, que anticoagulantes exerce un effecto benefic. Tamen, le comparation del severitate del morbo in le tres gruppos de casos indica que le casos non-tractate in le presente serie esseva plus grave. Il es possibile que iste factor explica le differentias del mortalitate.

7. Le apparente augmento del phenomenos hemorrhagic e le absentia de un melioration del mortalitate o del incidentia de thromboembolia inter le casos in que heparina esseva immediatemente addite al therapia anticoagulante pare justificar le conclusion que le uso de heparina non es profitabile.

SUMMARIO IN INTERLINGUA

(See page 676 for original article)

Le Tractate Lesion Pulmonar e Su Bacillo Tubercular
III. Studios de Susceptibilitate a Drogas

Esseva studiate le validitate que tests preoperatori del susceptibilitate a drogas possede como indice del requirimentos drogal pro interventiones chirurgic. Le material del studio veniva ab 105 resectiones e includeva 236 lesiones: cavitates aperte, cavitates claudite, cavitates de stadio final, tuberculos, e tuberculomas. Omne le patientes habeva essite tractate con streptomycina (SM), acido para-aminosalicylic (PAS), e hydrazido de acido isonicotinic (HIN), individualmente o in combination. Le studios de sensibilitate esseva restringite a iste tres drogas.

1. Esseva executate 181 comparationes del sensibilitate in le ultime positive cultura obtenite ab le patiente ante le operation con le sensibilitate de bacillos prendite ab le resectionate lesiones. In 72 pro cento del comparationes il se tractava de cavitates aperte. In 66 pro cento de iste casos le comparation revelava accordantia.

2. Le accordo inter le observationes de susceptibilitate in le culturas pre-operatori e le observationes de susceptibilitate in le bacillos derivate ab tessutos resectionate esseva positive in 67 pro cento de omne le typos de lesion in combination.

3. Susceptibilitate a drogas ante le operation esseva constatate in 69 pro cento del observationes, durante que culturas ab lesiones resectionate monstrava susceptibilitate in 48 pro cento del casos. In iste ultime gruppo il habeva un augmento de 21 pro cento in le resistentia.

4. Inter omne le lesiones de tessuto resectionate, le cavitates aperte forniva le plus grande numero de propagabile bacillos tubercular, si reguardo al stato preoperatori del sputo. Inter omne le lesiones, le tuberculos forniva le plus grande numero de culturas negative, sin reguardo al stato bacteriologic ante le operation.

5. Cavitates de stadio final (bacteriologicamente negative) esseva trovate in 34,5 pro cento del resectiones ab negros e in 16,7 pro cento del resectiones ab blancos. Il esseva constatate que iste differentia de 17,8 pro cento es statisticamente significative. Le alte incidentia de cavitates de stadio final inter negros e inter blancos es sin dubita conditionate per le selection del casos.

THE TREATED PULMONARY LESION AND ITS TUBERCLE BACILLUS*
III. DRUG SUSCEPTIBILITY STUDIES

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Prior to the antituberculosis drug era, pulmonary resection procedures were rarely undertaken and then only with great trepidation because of dissemination. The drugs evolved during this period have made possible the prevalent usage of surgery in the treatment of tuberculosis but have also entailed many problems, one of which is the reliability of preoperative susceptibility tests in selecting chemotherapeutic coverage at operation. Much attention has been focused on preoperative chemotherapy and, especially, has been linked to the pathology and bacteriology of resected lesions (Loring and Vandiviere[9], Falk, Tucker and Kaufman[5] and Vandiviere *et al.*[17]), including the morphological and metabolic condition of the tubercle bacilli so contained (Vishwanathan *et al.*[18], Yegian[21] and Granville *et al.*[6]).

Acid-fast microörganisms contained in various tuberculous lesions respond in varying ways to investigative procedures in the laboratory. Most microscopically visible tubercle bacilli grow rapidly on culture and demonstrate virulence; some, though they grow, fail to produce progressive disease and thus are avirulent for laboratory animals; some demonstrate no metabolic activity or growth without special laboratory procedures, and still others fail to show any indication of life in spite of application of all known techniques.

Several theories have been proposed to explain the interaction of the drug, the lesion and the host to produce these phenomena (Vandiviere *et al.*[17], Canetti[3] and Beck and Yegian[2]). Attempts have also been made to explain resistance or sensitivity of bacilli recovered from resected tissue on the

*This study and studies 1 and 2 in the series stem as an outgrowth from a research grant provided by the Medical Research Committee of the American Trudeau Society, Medical Section of the National Tuberculosis Association through a specific bequest from the estate of Nanette W. Chesebrough.

basis of duration of positive or negative sputum prior to operation (Wayne and Salkin[20]). However, less attention has been directed to preoperative susceptibility tests and chemotherapy as correlated with the type lesion resected and the tubercle bacilli recovered therefrom.

Physicians endeavor to keep in reserve one drug to which the patient's microörganisms are "sensitive" in order to "cover" surgical procedures. Because of the reliance placed in preoperative determinations of drug susceptibility of organisms from the sputum of patients considered for surgical excision, and because of the concept that "a patient is either 'sensitive' or 'resistant'" the present study was undertaken. The comparison of drug susceptibility tests on 1) preoperative secretions and 2) tissues from operation is studied in relation to preoperative chemotherapy and classification of lesion at dissection with its resultant tubercle bacilli.

Materials and Methods. This study includes the resultant tissues from 105 operations. These contained 236 lesions which include the cavity—open, closed and end-stage (open-healed) and solid lesions commonly called tuberculoma and tubercle. All patients had been on antituberculosis chemotherapy and bed-rest for different lengths of time prior to operation. The duration of drug therapy was variable and was in various combinations. Streptomycin (SM), para-aminosalicylic acid (PAS) and isonicotinic acid hydrazide (INH) were used and a scattering few patients had pyrizinamide, cycloserine or viomycin.

The method for handling and examining surgical specimens and for culturing bacteriological samples from such specimens has been described previously (Vandiviere *et al.*[17]) and the five types of lesions discussed, including open, closed and end-stage cavity, tubercle and tuberculoma were defined. Preoperative determinations of drug sensitivity were done on the last culture of tubercle bacilli isolated from the sputum (or gastric contents) before operation. Bacilli isolated from secretions before operation and tissue removed at operation were tested with the incorporation of the drugs into Lowenstein-Jensen's medium (Subcommittee on Laboratory Methods[14]). The range of SM used was 3, 10, 100 and 500 mcg. per ml.; PAS—1, 10 and 50 mcg. per ml.; INH—1, 5 and 10 mcg. per ml. of media. In this study bacilli which grew in the presence of less than 10 mcg. of SM per ml. of media were considered sensitive; those which grew in the presence of 10 mcg. per ml. or more of SM were regarded as being resistant; growth below 10 mcg. per ml. of PAS was deemed sensitive; growth at 5 mcg. of INH per ml. or greater was interpreted as resistant.

Results. Table 1 presents the number of lesions containing bacilli capable of reproduction, along with the number and per cent of lesions that produced conventional (8 weeks) and delayed growth. Among the 236 resected lesions studied, 77 (32.6%) contained viable bacilli as proved by culture. Of these 77 lesions which yielded bacilli on culture, 65 (84.4%) produced colonies in 8 weeks or less and 12 (15.6%) required extended incubation for growth. (The difference in numbers of lesions as described here and in previous publication II is necessary because this study must include only those patients with susceptibility studies obtained prior to operation.) The period of incubation required to produce growth of tubercle bacilli from the closed cavity is in sharp contrast to that required for microörganisms recovered from open cavity to grow and so for the tubercle and tuberculoma. All cultures which have failed to yield propagable bacilli have been incubated at least 6 months. No cultures from closed cavities revealed growth of tubercle bacilli at 8-weeks' incubation, while more than 95% of all other lesions which were positive by culture produced colonies in 8 weeks or less. Due to extremely variable drug therapy, no attempt has been made to correlate these data with treatment.

SUSCEPTIBILITY STUDIES. The compar-

ative results of drug susceptibility tests on resected tissues are presented in Table 2. These were pulmonary lesions from 105 operative cases who received SM, PAS or INH or a combination of them. Only lesions containing propagable tubercle bacilli having preoperative drug susceptibility data available could be included in this study. Therefore, the cases suitable for inclusion were reduced to 51 or a total of 66 lesions. A total of 181 comparisons were made. The drug susceptibility tests of bacilli from each resected lesion were compared with the susceptibility results of the same patient's bacilli isolated before operation for each drug he received preoperatively. The 181 comparisons of these tests for susceptibility to SM, PAS and INH agree in 67% of the cases. The increase in resistant populations from resected tissue accounted in large part for the 33% disagreement. Of the comparisons, 69% were sensitive preoperatively and of those recovered from the resected tissue only 48% were sensitive. Approximately 31% had resistant bacilli preoperatively but, on study of the resected specimens, 52% yielded resistant bacilli. Thus, a difference of 21% was found between the number of observations of sensitivity preoperatively on sputum or gastric contents and on the tissues removed. This 21% represents the increase in populations of resistant bacilli from resected tissue. The data in Fig. 1 indicate that resistance to INH, both preoperatively and operatively, is somewhat greater than to SM and PAS.

A comparison of drug susceptibility

TABLE 1.—THE DISTRIBUTION OF POSITIVE TUBERCLE BACILLI CULTURES FROM RESECTED LUNG SPECIMENS

Type Lesion	*Number Lesions*	*Number Positive*	*% Positive*	*Growth in < 8 Weeks*		*Growth After 8 Weeks*	
				No.	*%*	*No.*	*%*
Open	67	53	79.1	52	98.1	1	1.9
Closed	27	9	33.3	0	0	9	100.0
Tuberculoma	34	7	20.6	6	85.7	1	14.3
Tubercle	80	8	10.0	7	87.5	1	12.5
End-stage	28	0	0	0	0	0	0
Total	236	77	32.6	65	84.4	12	15.6

TABLE 2.—AGREEMENT SUMMARY OF DATA ON DRUG SUSCEPTIBILITY OF TUBERCLE BACILLI SECRETED PREOPERATIVELY AND RECOVERED FROM SURGICAL SPECIMENS

Susceptibility Data Preoperative vs. °Operative	*Number*		*%*	
Agree	121		66.9	
Disagree	60		33.1	
Total	181		100.0	
	Preop.	*°Oper.*	*Preop.*	*°Oper.*
Sensitive	125	87	69.1	48.1
Resistant	56	94	30.9	51.9
Total	181	181	100.0	100.0

°Lesion Susceptibility Data

determinations of bacilli in preoperative secretions and those in removed tissue is shown graphically in Fig. 1. The results are broken down into type of lesion and kind of drug. An entry is made for each lesion, and for each drug susceptibility test of bacilli obtained before operation and those recovered at operation. Therefore, a single lesion may be listed three times if the patient from whom the lesion was taken had been treated with three drugs.

Of all comparisons, 130 (72%) were

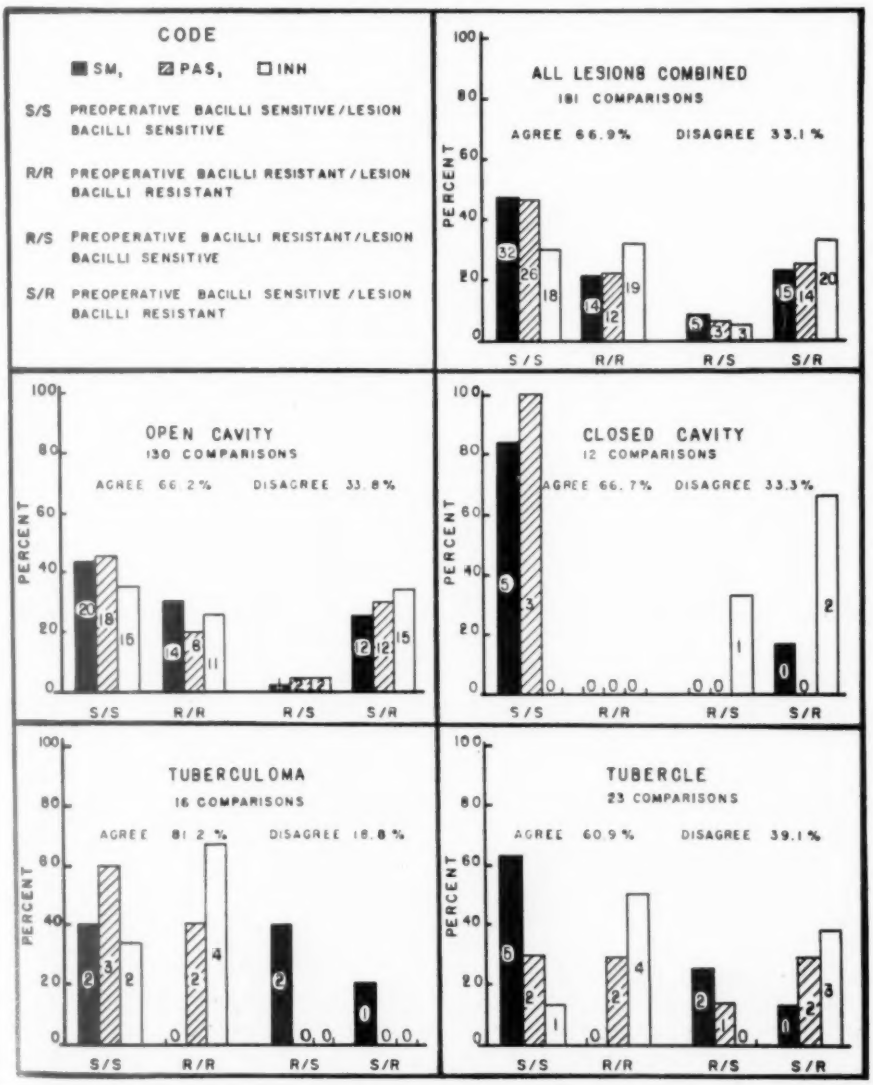

Fig. 1.—Comparison of preoperative drug susceptibility tests and susceptibility of positive cultures from lesions of patients receiving SM, PAS, and INH. (Numbers within columns represent number of observations.)

made on open cavities and 12 (7%) on closed cavities. The percentage agreement for both open cavities and closed cavities approximated very closely that for all lesions combined.

Agreement between sensitivity or resistance of bacilli obtained preoperatively and those obtained from the tissues was about equal for all in the case of SM (70%) and PAS (69%), while the percentage agreement for INH (62%) was a little lower. From open cavities, greatest agreement was demonstrated with SM; then PAS and INH followed in order. In the case of closed cavities, all of which had sensitive bacilli, 67% agreement was demonstrated. The agreement (operative and preoperative sensitivity) for the tuberculoma was 14% above the percentage agreement for all type lesions combined and in the tubercle was somewhat less; however, these by definition would not have contributed to preoperative susceptibility studies.

In Fig. 2, 192 lesions from 78 resected specimens are illustrated according to lesion classification and bacteriological results from the tissue study. Of 192 lesions, 128 (66.7%) were negative and 64 (33.3%) were positive. The relationship of preoperative bacteriology to that of excised tissue within given type lesions is shown. Some resected specimens contained both positive and negative lesions.

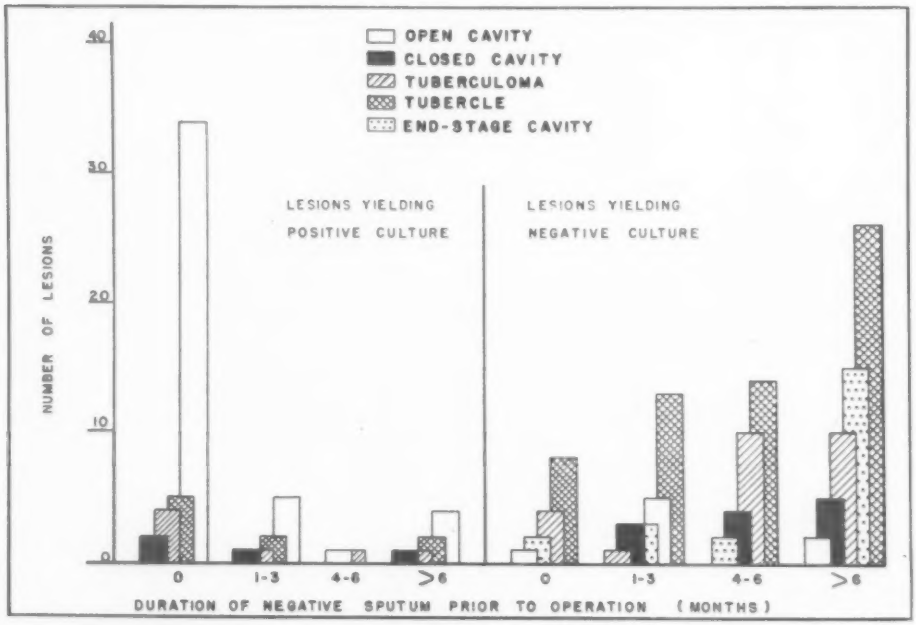

Fig. 2.—The relationship of preoperative bacteriology and presence of culturable bacilli in excised lesions.

Most of the lesions from patients who were positive at the time of operation presented classical open cavities. There were more lesions containing culturable tubercle bacilli from patients whose sputum was positive at the time of operation than

from those whose sputum was negative. No appreciable differences in the number of propagable bacilli-containing lesions were found, regardless of whether the patient's sputum was negative for one month or more than 6 months before operation (see Fig. 2). (It should be recognized that all patients for surgery were considered to be stable by roentgenogram for a period of 3 months, except in a very few salvage cases.) More open cavities produced viable tubercle bacilli than any other type of lesion, regardless of preoperative bacteriological studies. Yet there is a positive relationship between the duration of negative sputum prior to operation and the total number of *negative* lesions resected. As would be expected, tubercles predominated, regardless of duration of negative sputum prior to operation. End-stage cavities were conspicuous among the culturally negative lesions (22 of 22) as were the tuberculomatous lesions (25 of 32).

RACE AND BACTERIOLOGY OF RESECTED TISSUE. An attempt has been made to demonstrate whether a relationship exists between race and results of bacteriological exploration of removed tissues. Of a total of 100 resected specimens, 58 were from Negro patients and 42 were from whites. Of those from Negro patients, 41.4% revealed one or more lesions which contained viable bacilli as compared with 38.1% from white patients. This difference of 3.3% between white and Negro patients is within limits of probability. Resected specimens with and without propagable tubercle bacilli from white and Negro patients were further subdivided into categories of duration of negative sputum prior to operation but this illustrated no point of special interest.

It was noted that end-stage cavities occurred more frequently in resected tissues from Negro patients than from whites. A tally of these observations appears in Table 3. From the 58 specimens from Negro patients, 20 (34.5%) contained end-stage cavities as compared with only 7 (16.7%) from whites. The ratio of resection from Negroes to that from whites is 1.4/1 while the ratio of the end-stage cavity found in Negroes to that in whites at resection is 2.9/1. Are Negroes more prone to develop end-stage cavities than Caucasians? This difference was tested statistically and found to be significant.

TABLE 3—COMPARISON OF END-STAGE CAVITIES IN NEGRO AND WHITE PATIENTS

Race	*Number of Resections*	*Number of End-stage Cavities*	*% End-stage Cavities*
White	42	7	16.7
Negro	58	20	34.5
Total	100	27	27.0

Chi square = 3.07 (92% probability level)

Discussion. The reliability of preoperative susceptibility tests as they might pertain to "drug coverage" in operation is a pertinent question. Observations on drug (SM, PAS and INH) susceptibility tests of tubercle bacilli obtained before and after operation revealed a 21% increase in resistance of those removed by operation. Thus, the surgical cases involved might not be covered by drugs to which many of the patient's organisms were sensitive as was indicated by calculations on preoperative data. Armstrong and Walker[1] stated that sensitivity testing methods generally used do not determine whether the presence of sensitive organisms among resistant ones is an indication that resistance is associated only with the area of the lung from which the sputum came or is a phenomenon representing all areas of the lung.

Others (Turnbull and Stewart[16] and Stewart[13]) have shown that variations in the degree of resistance and in the susceptibility of individual colonies from a particular culture occur frequently. Such reports strongly support the belief that preoperative sensitivity does not give a full picture of the susceptibility of bacilli harbored in the patient's lesions. Obviously, preoperative sensitivity will provide a more accurate picture of the microörganisms which will be present in removed open cavitary tissue than from the closed lesions. Perhaps it is less important from the clinical point of view to predict sensitivity of tubercle bacilli in closed cavities, tubercles and tuberculomas because these may be least apt to "spill" tubercle bacilli with or without surgical manipulation.

Wayne and Salkin[20] noted a positive relationship between recency of tubercle bacilli in the sputum and their presence in the resected tissue. Not only did this condition exist in the present study, but those lesions from patients whose sputum was positive at operation contained at least one open cavity with propagable bacilli.

The sensitivity of bacilli from resected open cavities and preoperative sensitivity may represent microörganisms having common progenitors, and one would expect agreement of the order found. Good agreement was also observed between preoperative susceptibility tests and those tests on bacilli from closed cavities. In these cases there were instances in which the preoperative data were based on lesions open and draining immediately prior to operation. In other cases the preoperative data were probably from sputum obtained prior to closure of the examined lesion. It seems reasonable that comparisons based on the former would give less agreement than when based on the latter, but data are insufficient for further selectivity to evaluate this hypothesis. It has been shown previously (Vandiviere *et al.*[17]) that a majority of tubercle bacilli from closed cavities are sensitive to drugs, and it was suggested that lack of conditions necessary for normal metabolism possibly exists in these cavities, causing the respiration of the bacilli present to remain at a low level where inhibitory concentrations of drugs might fail to be effective. These statements may be applicable to granulomatous lesions also. Bacilli with caseum and engulfed in fibrous and "granulation tissue," while sensitive or resistant, may remain so, due to the above conditions, or effective concentrations of drug may never reach them. Among the smaller closed lesions (tubercles), most were negative and could have been rendered so by host-resistance and therapy before this type of lesion progressed to more extensive damage. Bacilli in the tuberculomas might be expected to appear dormant and require extended incubation for growth, but this was not so in most cases. Approximately 79% failed to grow (at 8 weeks or on extended incubation), but of those that grew, 6 of 7 did so in 8 weeks. The number which failed to grow falls between the data on tubercles (90% negative) and closed cavities (67% negative), but the rapid growth of viable bacilli from tuberculomas and tubercles approaches the open-cavity data.

End-stage cavities, which were all negative, were most often from patients whose sputum had been negative for more than 6 months prior to operation. Two patients who were positive at the time of operation revealed end-stage cavities, but these were patients with a long history of tuberculosis whose resected tissue also revealed classical open cavities. One patient yielded bacilli that were sensi-

tive and the other, cultures that were resistant to all drugs preoperatively. Possibly, the cavity reached its end-stage of healing before the bacilli became resistant, and the disease progressed in other areas of the lung where resistance developed. It must be recognized that there were gradations from classical open cavities to the end-stage cavity, but the dissector did not classify any as end-stage unless the lining was smooth, slick, shiny and thin-walled without any visible necrotic foci. Each of these were verified by subsequent pathological examination.

In keeping with the observations of Johnsen and Hewitt[7] and Russell *et al.*[12], end-stage cavities in this series were observed to occur most often in Negro patients whose race perennially has presented lower natural resistance to tubercle bacilli than white people have. In the Negro, formation of the "end-stage" cavity appears in greater proportion than among whites, and this favorable type of healing surprises when it develops in this race. It is difficult to align "poor resistance" with favorable end-stage cavitation unless on the basis of more massive caseation and slough on part of the host which is associated in proper time relationships with prompt effect of the drug upon the bacilli. If limiting influence of the drugs operates at the time when extensive excavation of the poorly resistant and caseous tissue occurs, the issue could result in creation of large cavity (having but little necrotic tissue left) which could heal by scant scar because progression of the disease had meantime been resisted by the drugs.

The presence of 27% end-stage cavities (see Table 3) is considerably higher than the end-stage cavity incidence in previous reports (Katz and Klopstock[8] and Thompson[15]). It should be recognized that this is not in disagreement because most cases herein reported were highly selective in their admission, as approximately 95% of them were referral cases due to drug failure or surgical need, or both.

It is generally known that bacterial resistance to INH develops in a large proportion of patients who are treated with this drug alone (Dye, Lynch and Brees[4], Wallace *et al.*[19] and Medical Research Council[10]). The Medical Research Council[10] has reported on the rapid development of resistance to INH and noted that lack of progress both clinically and radiologically was associated with emergence of resistance. The same group (Medical Research Council[11]) reported slightly higher incidence of resistance to INH than to SM from patients treated with combined INH and SM. The present work shows resistance of bacilli cultured from all specimens was greater for INH in combination than for SM in combination. The increase in resistance between preoperative and resected cultures is further evidence of a decided tendency of tubercle bacilli to develop resistance to INH, even after the emergence of the bacilli from the sputum has ceased.

Summary. The reliability of preoperative drug susceptibility tests as an indication of "drug coverage" for surgical intervention has been studied. A total of 236 lesions, the cavity—open, closed and end-stage-tubercle and the tuberculoma, from 105 resected tissues were studied. All patients had been treated with one or a combination of the following drugs: SM, INH or PAS. Sensitivity studies concerned these drugs only.

(1) Comparisons (181) were made of sensitivity of a patient's last positive culture before operation and bacilli recovered from his resected lesions. Open cavities accounted for 72% of the

comparisons and revealed 66% agreement.

(2) Sixty-seven (67) per cent agreement between preoperative culture susceptibility data and drug susceptibility of bacilli recovered from removed tissue was observed for all lesions combined.

(3) Preoperative drug susceptibility was found in 69% of the observations and cultures from resected lesions showed 48% susceptibility. The latter group revealed a 21% increase in resistance.

(4) More resected open cavities yielded propagable tubercle bacilli than any other lesion regardless of preoperative sputum status. More tubercles were negative than other lesions regardless of preoperative bacteriological assay.

(5) The end-stage cavity, bacteriologically negative, was found in 34.5% of the resections from Negro patients and in 16.7% of resections from whites. This difference of 17.8% was found to be statistically significant. The high incidence of end-stage cavities in both races doubtless relates to selectivity of cases.

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(Interlingua on page 675)

ACUTE GENICULAR ARTHRITIS SIMULATING THROMBOPHLEBITIS

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It is not generally recognized that uncomplicated arthritis of the knee may be associated with signs which can lead to an erroneous diagnosis of a coincident thrombophlebitis of the deep veins of the leg. This diagnostic pitfall is worthy of note because thrombophlebitis of the legs is commonly considered an indication for the use of anticoagulants or vein ligation, procedures which at best entail expense and inconvenience and at worst are followed by dangerous sequelae. Our attention was drawn to this problem by the two cases presented below. Subsequently an intensive study was made of the frequency with which signs usually indicative of deep thrombophlebitis of the leg were found in patients who had arthritis of the knee.

Case Reports. CASE 1. A white male, 40 years of age, had a 2-year history of rheumatoid arthritis characterized by pain in his proximal interphalangeal joints, left shoulder, right knee and left foot. There was a history of two episodes of thrombophlebitis of the right calf. At irregular intervals of 30 to 120 days he received intra-articular hydrocortisone for extreme right knee disability. On April 22, 1955, thirteen days after an injection into the right knee, the patient was seen because he was concerned over the return of what had previously been considered thrombophlebitis of the right leg. He complained of right knee and calf pain and ankle edema. Examination disclosed swelling of the right knee which had been intermittently present during the preceding year. Moderate edema of the ankle was detected. There was tenderness on pressure on the calf and somewhat greater tenderness on pressure over the posterior capsule of the knee. When Homan's test was performed, the patient complained of pain in the upper third of the calf and behind the knee. Right knee flexion was limited to 90 degrees and was painful. A diagnosis of thrombophlebitis was made and the patient started on daily intramuscular injections of heparin and placed at bed rest. After a week of this regimen there was no change in the physical signs. Because of this persistent course it was thought that the symptoms and signs might be due entirely to arthritis of the knee. Accordingly, 50 mg. of hydrocortisone were injected into the right knee after 30 ml. of cloudy fluid were aspirated. The total white count of the fluid was 22,000 per c.mm., and when acetic acid was added, the mucin formed a cloudy solution with a few small clumps. Within 24 hours the patient's symptoms had entirely disappeared. The ankle edema and the calf and knee pain completely regressed. There was still some residual knee enlargement. The right knee could now be flexed to 120 degrees. Homan's test was negative. Calf and posterior capsule tenderness were no longer present.

In view of the prompt disappearance of symptoms and signs after the intra-articular injection of hydrocortisone, it would seem that the diagnosis of thrombophlebitis was erroneous and that the signs were due solely to the arthritis of the knee.

CASE 2. A colored female, 55 years of age, was known to have rheumatoid arthritis of several years' duration with multiple joint involvement including the right knee and ankle. She was receiving salicylates and prednisone, 5 mg., t.i.d. orally. She was seen in July, 1956, complaining of right calf pain and increased pain in her right knee. Examination disclosed the multiple deformities of rheumatoid arthritis. Her right knee was larger than it previously had been and was warm. There was pain and limitation on flexion of the knee. Calf tenderness and a positive sphygmomanometer cuff pain test (Lowenberg[2]) at 130 mm. of mercury were demonstrated. In addition, there was tenderness when pressure was made over the posterior capsule of the knee. Slight ankle

edema was present. Homan's test was negative.

It was apparent that an exacerbation of the arthritis of the right knee had occurred. Because of the previous experience with arthritis simulating thrombophlebitis, 50 mg. of hydrocortisone were injected into the right knee after aspiration of a small amount of cloudy fluid. In 24 hours the signs of arthritis of the knee had decreased greatly, as had the calf tenderness. The sphygmomanometer cuff pain test was now positive at 210 mm. of mercury. The patient had omitted her oral prednisone for 24 hours and was advised to restart it. When seen 3 days later there was no calf tenderness and only slight ankle edema.

2. Calf tenderness. This was elicited by exerting bilateral pressure on the calf muscles. Frequently the sphygmomanometer cuff pain test was used to verify the tenderness.

3. Posterior knee tenderness. This was elicited by exerting pressure at the popliteal space.

4. Pedal edema.

5. Pain on flexion of the knee. This sign was elicited with the patient supine, the thigh held stationary at 90 degrees of flexion, and the knee flexed to its maximum degree. In the presence of active arthritis of the knee, pain in the knee was invariably produced by the maneuver.

TABLE 1.—PHYSICAL FINDINGS IN 67 CASES OF GENICULAR ARTHRITIS

Type	*No. of Cases*	*Homan's Sign*	*Calf Tenderness*	*Post Capsule Tenderness*	*Pedal Edema*	*Pain on Flexion of Knee*
Degenerative	27	2	2	3	2	27
Rheumatoid	30	6	10	14	6	30
Traumatic	2	1	0	0	0	2
Serum sickness	1	0	0	0	0	1
Gout	6	0	2	2	0	6
Undiagnosed	1	0	0	0	0	1
Totals	67	9	14	19	8	67

Sixty-seven patients with arthritis of the knees were examined carefully with particular reference to the occurrence of signs frequently associated with thrombophlebitis of the deep leg veins of the calf. Six had gout, 30 had rheumatoid arthritis, one had serum sickness, 27 had degenerative arthritis, 2 had acute traumatic arthritis, and in one the diagnosis was uncertain. None of the patients was thought to have thrombophlebitis because of the persistence of the findings, sometimes for months, only to disappear when the arthritis subsided. Furthermore, the common sequelae of thrombophlebitis, namely, varicosities, persistent dependent edema, and emboli, were not noted. The signs particularly sought were:

1. Pain in the posterior leg on dorsiflexion of the foot (Homan's sign).

The findings are tabulated in Table 1. All of the patients had pain on flexion of the knee in keeping with their diagnosis of active genicular arthritis, as mentioned previously. It is also apparent that the patients with rheumatoid arthritis of the knee were most likely to present signs suggestive of thrombophlebitis. A positive Homan's sign or calf tenderness was observed in approximately 30% of these patients.

Discussion. When a patient who has arthritis of the knee is seen with calf tenderness or posterior leg pain on dorsiflexion of the foot, there may be considerable difficulty in deciding whether or not there is a coincident

thrombophlebitis of the deep veins of the leg. When these signs are due solely to the arthritis of the knee, Homan's test causes pain predominantly behind the knee. At times patients point to the origin of the calf muscles, and on direct questioning state they feel "pull" more than "pain." When calf tenderness is present, there also is tenderness over the posterior capsule of the knee which exceeds that noted on pressure on the calf. Finally, injection of hydrocortisone into the affected knee is followed by disappearance of the signs suggesting thrombophlebitis.

Summary. A positive Homan's sign, calf tenderness, and pedal edema, signs usually suggestive of thrombophlebitis of the deep veins of the leg, were encountered in a significant proportion of patients with acute genicular arthritis. Two case histories illustrating this diagnostic problem are presented. Suggestions are made for determining whether the signs are due to the arthritis or to an associated thrombophlebitis.

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SUMMARIO IN INTERLINGUA

Acute Arthritis Genicular, Simulante Thrombophlebitis

Un positive signo de Homan, sensibilitate sub pression in le suras, e edema pedal, iste signos que usualmente suggere le presentia de thrombophlebitis del venas profunde del gamba, esseva trovate in un proportion significative de patientes con acute arthritis genicular. Es presentate le historias de duo casos que illustra iste problema diagnostic. Es facite proponimentos que pote servir a determinar si le signos es le effecto de arthritis o de un associate thrombophlebitis.

PROGRESS
OF
MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF
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NEWLY ISOLATED VIRUSES AS CAUSES OF DISEASE

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THE field of virus research, especially as it relates to the newly isolated viruses, is in the state of chaos which must be expected from its rapid expansion and its wide diversification. A virus isolated in one continent may be and often is re-isolated independently and simultaneously in another continent. Each agent receives names conferred by its independent discoverers and volumes may be published about each and its numerous relatives before the interested observers get together to decide on standards of nomenclature, possible relationship to disease, and the like[20,34]. The meeting and sorting place is "the literature" which becomes more and more tangled before deliberate effort is made to sort it out.

This rapid expansion is due largely to the reintroduction of tissue cultures in virus research by Enders, Weller and Robbins[37] and to their demonstration that the techniques required for tissue culture are simple enough for any bacteriologist to handle. Add to this the by-products of such large-scale research projects as those supported by the National Foundation for Infantile Paralysis for analysis of the efficacy of the Salk vaccine, and the current spate of information is easy to understand.

Tissue cultures were not new in virus research[137], but Enders, Weller and Robbins developed them into a simplified practical tool. They pointed out that even in the test tube the *in vivo* host specificity for a specific virus persists[121]. Rabbit fibroblasts, for instance, will not support the growth of poliovirus in tissue culture,. but human fibroblasts will. They and others[99,125] have expanded this observation of host specificity and have shown that human fibroblasts will support growth of certain viruses while human epithelium

growing out in the same culture tube from the same bit of human tissue will not. They showed further that virus attack on some cells will destroy the cells, often in typical fashion, and that the "cytopathic effect" can be identified in unstained preparations under the microscope, or reflected in changes in the pH of the feeding solution as the host cells are destroyed[37,120]. They demonstrated the natural corollary to this, that the cytopathic effect could be prevented by the presence of specific neutralizing antibody to the specific virus (polio) being studied[120]. And still further, they showed that material as crude as feces could be studied in tissue culture with the help of antibiotics.

With this stimulus knowledge of viruses grew rapidly. As use of tissue cultures became general, even more simplified methods were introduced. Scherer, Syverton, and Gey[130] developed cultures of human malignant cells which grow rapidly on glass without the aid of plasma clot and which can be removed from the glass with trypsin, counted, and distributed to hundreds of other culture tubes, bottles or plates in any desired quantities. Following this, Dulbecco and Vogt[27] showed that the plaque techniques already known to the bacterial virus field are applicable to animal viruses, and consequently new accuracy and ease of titration was possible. The virus in single plaques or "colonies" can be studied as pure lines (not mixtures), and in addition, the plaques produced by various viruses are often characteristic in size, shape of outlines and time of appearance. Plaque characteristics together with tissue specificity and the use of specific immune serum to prevent plaque formation are of obvious import for the quick identification or classification of a new agent.

There is another development which is of growing importance and which has produced some interesting contributions worthy of note by clinicians. Rowe *et al.*[126], in searching for a readily available human cell as host for their virus studies, grew adenoid tissue removed from children in routine operations. After an incubation period some of their "normal" cultures showed cytopathic changes and grew several strains of viruses which could be passed serially and have since been called the adenovirus group. Subsequently they showed that the "salivary gland virus" could also be grown from their "normal" tissues[125]. A similar "induction" of growth of hidden or latent viruses occurs with monkey kidney cells which can produce the so-called "foamy agent" demonstrated by Rustigian *et al.*[128]. It is probable that the more familiar but still unexplained eruption of fever blisters following "induction" by sunlight, fever, and the like, is a reflection of the existence in the tissues of herpes simplex in a similar latent form. It may be that such mechanisms are quite common and that the persistence of virus and hence of antigen in the tissues provides part of the answer to the permanence of immunity to many virus diseases.

The true import of the latency phenomenon and its relationship to permanent immunity and the carrier state is not yet understood, nor is the simpler problem of the relationship of many of the new groups of viruses to the diseases in the course of which they are found. The mere finding of the agent in the pharynx or especially in the stools of a patient is, of course, no proof of its etiologic relationship to the disease. Many of the newly isolated viruses have been shown to exist in the stools of a large proportion of a clinically healthy population in certain seasons[56,106,115] and can, therefore, be present in the course of disease by chance. Etiologic relationship with disease becomes more clearly estab-

lished only when association has been shown to be unduly frequent in different parts of the world, when antibodies to the agent regularly develop in the course of the illness, when the agent is isolated from "inner" parts of the body like the blood stream or cerebrospinal fluid and when on passage to others it reproduces a similar disease picture. Such etiologic relationship is becoming more or less firmly established with several of the new agents. These will be taken up in groups arranged by similarity of disease picture as far as possible and where this seems unclear, by virus group.

VIRUSES PRODUCING EXANTHEMATOUS DISEASES. *Measles.* For years sporadic and probably successful attempts to grow measles virus in hosts other than man have been reported[3,110,113], but the agent was difficult to handle and in each case was lost. In 1954, Enders and Peebles[35] reported isolation in roller tubes of human kidney tissue of an agent which produced constant cytopathic changes with the formation of large multinucleated giant cells, most of the nuclei of which contain eosinophilic inclusion bodies. The agent could be isolated from throat washings and blood of early measles cases with ease and has since been grown successfully in other laboratories in many different types of human and monkey cells[12,24]. The cytopathic effect is prevented by the presence of convalescent human measles serum but not by the serum of patients in the acute phase of the disease. Specific complement fixing (C.F.) antigen released into the fluids feeding the infected tissue cultures has been used to show rise in C.F. antibody during natural human disease and during induced monkey infection[32,36]. Virus has been isolated from the blood stream in a total of 8 patients with typical measles in two different years, 1954 and 1955, and from the lung of a fatal case. Further, inoculation of the 23rd tissue culture passage of the virus into cynomolgus monkeys produced a disease similar to that in man. The evidence seems conclusive that the newly isolated agent is the cause of human measles, and further, that a useful tool is at hand with which to study measles infection and answer the burning questions of duration of communicability, length of viremia, relationship to encephalitis, and others. In recently reported studies of the disease process[32,36,108], virus was injected intranasally and intravenously into cynomolgus monkeys. The incubation period was apparently 9 to 10 days, ending with the appearance of an exanthem which lasted 4 or 5 days. Viremia developed on the 5th to 7th day after inoculation and lasted for 2 to 5 days. C.F. and neutralizing antibody became detectable a few days after disappearance of the exanthem and titers rose rapidly. Not all monkeys injected developed a rash and one failed to develop either rash or viremia, but all did develop antibodies.

Recently Enders *et al.* report[36] that a long cultivated laboratory strain of measles virus will multiply in embryonated hens' eggs and seems to be multiplying in chick embryo tissue in tissue culture. If multiplication continues and if the cultivated virus is a good antigen, the way is clear to early production of a vaccine.

Rubella. Previous investigations of rubella have by necessity been carried out with volunteers[4] and monkeys[48]. Recently, Anderson[5] has produced cytopathic changes in monkey kidney cells and in human embryo cells using throat washings obtained 18 hours after onset of a typical case of German measles. Isolation required 4 blind passages in monkey kidney cells before a change was observed, and the change then consisted of an increase in the number of multinucleated areas over that found in controls. The increase

was evidently obvious but it is reassuring that he was able to transfer the cytopathogenic agent to human embryo tissue where it produced similar multinucleated areas which were not found in controls. Human convalescent serum from an earlier experiment in volunteers inactivated the agent and pre-infection serum did not. Further, the virus was not inactivated by undiluted convalescent serum from a case of rubeola.

The evidence is suggestive that the agent of rubella has been isolated in tissue culture, but this has not yet been confirmed or amplified.

Chickenpox. Several early efforts to isolate the virus of chickenpox produced typical intranuclear inclusion bodies in unnatural hosts, but multiplication of the agent beyond this stage could not be demonstrated[47,119]. In 1952, Weller[147] apparently succeeded in isolating the virus and a year later[144] reported its serial propagation. Following inoculation of vesicle fluid from typical cases into suspended cells of mixed human embryonic tissue, and later into roller tubes of human embryonic skin and muscle or foreskin tissue, small sharply delineated foci appeared. These grew slowly and consisted of rounded refractile cells containing eosinophilic inclusion bodies in the nuclei. Some multinucleated giant cells were present which also contained eosinophilic inclusion bodies in the nuclei. These cells were quite similar in appearance to those occurring in the typical lesions in man. Serial passage of the responsible agent is possible only when infected cells themselves are transferred to the subcultures. Cell-free feeding solutions removed from infected cultures are not sufficient. So far, this is a unique characteristic demonstrated only for the virus strains isolated from patients with chickenpox or herpes zoster.

Neutralization of the virus at first could not be demonstrated, possibly because of the protective close relationship between cell and virus indicated in its passage characteristics. Recently, in unpublished work referred to by Enders[32], Weller has shown reduction in number of foci by convalescent sera. In the same paper, Enders refers to serologic studies of patients by the complement fixation method using tissue culture fluids as antigen and demonstrating significant rising titers of antibody in convalescent serum. Furthermore, by the use of the fluorescent antibody technique Weller and Coons[146] demonstrated that the infected loci in tissue culture specifically take up convalescent serum and that this reaction does not occur with normal serum or serum from the acute phase of the disease.

Agents with the same characteristics have been isolated from the blood and vesicle fluid of 2 fatal cases of varicella and from the lung lesions of one of these[17]. There is strong suggestive evidence, therefore, that the virus of chickenpox has been isolated on repeated occasions in at least one laboratory. Confirmatory evidence from other laboratories and further study of the disease process itself by the new techniques have not been found in the literature.

Herpes Zoster. Much of Weller's work with chickenpox virus was carried out in parallel using vesicle fluid from typical cases of herpes zoster. As has been repeatedly demonstrated in the past with old techniques, these two agents are so similar as to seem identical with the methods now available. Tissue culture growth characteristics, cell pathology, passage characteristics and cross reaction with the fluorescent antibody technique and complement fixation reaction show no difference between them[148]. The relationship between these two viruses is still unknown, but there is nothing

so far incompatible with the frequently reported suggestion that herpes zoster may represent the results of induction of latent varicella virus in an individual previously infected with varicella.

Infectious Exanthem, "Unusual Exanthem," Boston Exanthem. This disease was first noted in Boston during the summer of 1951 and on investigation was found to be widespread throughout Massachusetts[99,101]. A similar illness occurred in Pittsburgh in 1954[98]. There was a high attack rate involving children and adults with an incubation period of 3 to 8 days. Disease was mild in children, usually beginning with fever followed by a pink maculopapular rash over the face, trunk, and extremities. There was moderate enlargement of lymph nodes of the head and neck and little sign of systemic disease. Symptoms were more severe in adults, with chills, severe headache, myalgia, and a lower incidence and conspicuousness of rash. Neva and Enders inoculated feces and throat washings of several of these patients into suspended cell cultures of human kidney tissue and passaged supernatant fluids to roller tubes of human embryo skin and muscle or human foreskin tissue. From the stools of 7 of these patients a group of cytopathogenic viruses were recovered, all but one of which destroyed fibroblastic cells but left undisturbed epithelial cells growing from the same bit of tissue in the same roller tube. The viruses could be easily propagated in tissue culture but were not pathogenic for suckling or 3-week-old mice. In a later report, Enders says[32] that these viruses were isolated from 24 of 27 cases studied, and that 3 isolations were from throat washings and one from the blood.

Six of the 7 original agents were closely related or identical as evidenced by growth characteristics and serological responses and were probably the causative agent of the disease described above in that, in addition to repeated isolations, including one from blood, a rise in neutralizing antibody occurred in all cases tested (except for one inconclusive test in which the titer end points were missed). Isolation of virus and demonstration of rise in antibody was reported for the Pittsburgh epidemic in 1954[98], a strong piece of confirmatory evidence in favor of a cause-and-effect relationship between virus and disease.

The viruses themselves have not been classified. Lack of virulence for suckling mice makes them unlike the Coxsackie group. While they seem unique, Enders states that the possibility "still remains that they may eventually be classified among certain of the Echo agents"[33].

Roseola Infantum. The seventh agent isolated in the Boston 1951 study was not serologically related to the first 6 and in retrospect, the patient from whom it was isolated had a different illness more compatible with roseola infantum than with "unusual exanthem"[100]. The 2-year-old child had a fever fluctuating up to 104.4° F. for 4 days, was not very ill, and on the 4th day when the temperature was 100.2° F. developed a maculopapular skin rash over the shoulders and chest. The virus isolated from the feces of this child produced unusual changes in a wide variety of human tissues in roller tubes with swelling and distortion of epithelial cells as well as fibroblasts, but destruction was quicker in epithelial cells. The patient's convalescent serum delayed cytopathic effect with regularity, but did not prevent it. A clear rise in C.F. antibodies was demonstrable, however, and there was no serologic crossing with the viruses of "unusual exanthem." The agent did not infect suckling mice. An entry in a paper by Huebner *et al.*[60] on adenoidal-pharyngeal-conjunctival agents

states that this "roseola" virus is immunologically identical with Type 3 adenovirus.

With the data at hand it is impossible to say more than that this disease may have been roseola and that the virus isolated during the infection may have caused it. This virus was not a common stool virus in the area in which it was isolated.

Fifth Disease. An epidemic of an acute exanthem resembling typical Fifth Disease or Erythema Infectiosum occurred in a grade school in Reading, Pennsylvania, in the spring of 1955. There were 67 cases involving all ages, but primarily those between 6 and 9 years. Over-all pupil attack rate was 14.4% with the third grade having the highest attack rate of 39%. Characteristically, the typical rash was often the first and only symptom with fever in only 6 of the 67. Werner *et al.*[149] report the rash as characteristic with little other description, and so presumably it was the usual symmetrical exanthem[87] starting on the face and spreading peripherally, becoming more marked on lateral surfaces of arms and legs and on the buttocks. The rash is made up of maculopapular spots which fade from the center to give a lace-like or "geographic" appearance. It blanches on pressure, is evanescent and was described by Werner *et al.* as being associated with physical activity. It persists for a week or 10 days or more and sometimes itches. The rash on the face tends to be confluent and swollen over the cheeks, often with sharply demarcated edges and often sparing the nasolabial region.

Werner *et al.*, using monkey kidney tissue culture, isolated 3 cytopathogenic agents from this epidemic, two from stools and one from throat washings. The cytopathic changes appeared only after 3 to 5 blind passages and were characterized by "the appearance of multinucleated giant cells, with a large inclusion-like area in the nucleus and margination of the chromatin." The changes were similar to those produced by measles virus and distinct from those of the "foamy virus"[128], found latent in monkey kidney tissue. With tissue culture fluids used as complement fixing antigens, it was possible to demonstrate in 5 of 9 cases a fourfold or more increase in titer of complement fixing antibody with convalescence.

The evidence sounds suggestive that the agent is related to this disease. Its relationship to measles or other viruses is still unknown. Not much more can be said until further information is forthcoming.

Nottingham Meningitis. This disease is mentioned here because it has sometimes been associated with an exanthem. It will be more fully discussed in the section on Aseptic Meningitis. In essence, it is a disease recently described in England[103], Florida[14], and South Africa[30], and which is characterized by stiff neck, headache, fever, varying degrees of myalgia, and by rash and lymphadenopathy characteristic of rubella. Not all epidemics described included the rash in the clinical picture. Possibly several diseases and etiologies are involved. An Echo type 9 virus has been isolated which is probably one of its causative agents.

VIRUSES PRODUCING "ASEPTIC MENINGITIS." From a group of 854 cases collected from 1941 to 1952, Adair, Gauld and Smadel[1] summarized the proportion of cases of aseptic meningitis which could be diagnosed by laboratory means as recently as 1952. Using serologic identification with acute and convalescent sera from typical cases sent to the virus laboratory of the Army Medical Service Graduate School, they concluded that approximately 9% of the cases of aseptic meningitis were

caused by lymphocytic choriomeningitis (L.C.M.) virus, 12% by mumps virus, 5% by herpes simplex virus, and 7% by leptospiras. Here, as in other studies, between two-thirds and three-quarters of the cases were of unknown etiology. The unknown quantity is being rapidly reduced as new viruses, or well-studied old ones, are incriminated as possible causes of aseptic meningitis.

Poliomyelitis. For years, most of the cases of aseptic meningitis occurring in the summer months have been called "nonparalytic polio." The virus and the disease have been studied so carefully in so many parts of the world that they are now thoroughly accepted as cause and effect. Polioviruses definitely cause aseptic meningitis, but not as frequently as was expected before laboratory diagnosis became practical.

Coxsackie Viruses. (Will be discussed as a group later).

The Group B members of the Coxsackie viruses are becoming generally recognized as a cause of aseptic meningitis. Group B strains have been isolated repeatedly in different parts of the world from stools of individuals with the disease[22,72,83,116,151], whereas they are rarely found in stools of normal persons. Antibody to Group B strains regularly increases during convalescence. Johnsson's study[69] of the spread of Coxsackie virus Group B, type 3, among members of families provides further epidemiological evidence for its etiologic role in aseptic meningitis in children as do his studies of the epidemiology of Coxsackie viruses in general in Sweden[73]. Finally, in reports from Sweden[42], Canada[28,94,116], South Africa[151], and the United States[62], there are now over 25 instances of the isolation of Coxsackie Group B strains from the spinal fluid of patients. Evidence now seems conclusive that Coxsackie B viruses can cause aseptic meningitis.

The evidence for Coxsackie A viruses is not so clear. Various observers have frequently found Group A, type 9 virus in the stools of aseptic meningitis patients and report antibody rises to it during convalescence[50,51]. Group A Coxsackie viruses are fairly widespread in healthy individuals in summer, however, and no report was found of isolation of the virus from spinal fluid. Consequently, more evidence will be needed before its role, if any, in aseptic meningitis is known.

Echo Viruses. Echo (enteric cytopathogenic human orphan[20]) viruses were found in large numbers and in different areas in the stools of patients being studied as part of the program determining the efficacy of the poliovirus vaccine. Echo viruses produce typical cytopathic effects in a wide variety of cell lines in tissue culture and, by means of this technique, have been isolated frequently in the last 2 years from the stools of patients with aseptic meningitis as well as from the stools of healthy individuals[56,71,114]. There are now at least 14 antigenic types, none of which had, until very recently, been shown to be related to disease. At a Conference on "Viruses in Search of Disease," held at the New York Academy of Sciences (May 24 and 25, 1956), mention was made in papers and discussion from at least 3 laboratories of frequent isolation of Echo 6 virus from the stools of patients with aseptic meningitis[77,79,95,138]. Since then, Davis and Melnick[23] from New Haven, and Karzon *et al.*[78] from Buffalo, have reported the isolation of Echo type 6 from the spinal fluid of such cases, Davis and Melnick with 3 isolates and Karzon *et al.* with 7. All the patients reported developed neutralizing antibody to Echo type 6 in convalescence. Other authors have

shown association, though in lesser numbers, of symptom complex with other orphan viruses, only some of which have been identified. Karzon isolated 3 more from spinal fluid which were untyped. Rhodes[116] from Toronto found 3 in spinal fluid, type not mentioned. Steigman *et al.*[136] isolated an orphan virus from the spinal cord of a patient thought clinically to have bulbospinal poliomyelitis. In a personal communication to Karzon, they report that this last virus has been identified serologically as Echo virus type 2.

Nottingham meningitis has been discussed at length in various issues of *Lancet*[7,88,91,109,139] over the course of the last 9 months. Discussion has been primarily in the form of letters, annotations and editorials, and is digested here in chronological order since it provides a good illustration of the vicissitudes involved in the developmental history of a "new" disease entity from its clinical recognition and description to ultimate identification of its etiologic agent.

Evidently the term "Nottingham Meningitis" originated in the lay press and was used in an early letter to the editor for the sake of simplicity[103]. In Nottingham, however, the disease was referred to as "Trent Valley Fever." One author reported from Jacksonville, Florida[14] that he had been calling it or a similar infection "Iceland Disease" (after the report of Sigurdsson *et al.* about an epidemic in Akureyri, Iceland[132]). These assorted reports vary somewhat in clinical description. Most describe patients with stiff neck, headache, fever, varying degrees of myalgia and with rash and lymphadenopathy characteristic of rubella. Cells in the spinal fluid varied from normal limits up to 2000 per c.mm., with as high as 50% polymorphonuclear leukocytes. Others[67], describe a disease with normal spinal fluid, severe headache, great emotional lability, nausea and vomiting, paresthesia and severe myalgia which progressed to weakness and perhaps paralysis, occasional urinary retention and a long drawn-out convalescence with frequent relapses but ultimate recovery. There are apparently all gradations between the two, suggesting that possibly several diseases and etiologic agents are involved. The editors of *Lancet*[7,88] make an effort to classify the clinical syndromes on the basis of spinal fluid changes and suggest the term "benign myalgic encephalomyelitis" for those with no cerebrospinal fluid changes. The division is highly artificial, but is as good as any until more information is available as to etiology.

Tyrrell and Snell[139] isolated 8 strains of a new virus from the stools and throat swabs of patients with Nottingham Meningitis. The new virus is pathogenic for suckling mice, giving striated muscle lesions similar to Coxsackie Group A lesions. Its tissue culture behavior is compatible with this group. It is not neutralized, however, by antisera against Coxsackie Group A, types 1 to 10, or Group B, types 1 to 4, or by antisera against three types of poliovirus and adenoviruses type 1 to 11. Specific neutralizing antibody developed to it in the serum of 7 of 8 patients tested, with a fourfold or greater rise in 5 of the 8.

A virus similar to that of Tyrrell and Snell has been isolated from similar cases by Crawford *et al.*[21]. Five agents were isolated from the stools of 10 patients, and clear-cut antibody rises to high titer were demonstrated in all cases but one (in which there were no cerebrospinal fluid changes). The 5 strains were closely related to each other serologically, but not related to polio, adenoviruses, three types of Echo virus, Coxsackie A or B, herpes

simplex, mumps, L.C.M., influenzas or the psittacosis group. They differed from the organism of Tyrrell and Snell in that they were not pathogenic for suckling mice.

In March, 1957, 3 articles[13,43,122] appeared in *Lancet* clarifying a good bit of the foregoing confusion. Boissard *et al.*[13] studied throat washings, stools and spinal fluid from 11 patients during the same epidemic of aseptic meningitis in England, and isolated a cytopathogenic virus from 6 of the 11 stools, 4 of the 10 throat washings, and 5 of the 9 cerebrospinal fluids.

Monkey antiserum to one of the new strains neutralized all of Boissard's new agents and also other agents recently isolated from aseptic meningitis cases in Nottingham, Coventry, West Germany, Toronto, and the United States[93], including the virus of Tyrrell and Snell and that of Crawford, both discussed previously. The specific antiserum neutralized also the Echo 9 prototype virus as did the serum of patients, thereby unifying a large seemingly heterogeneous group and placing it in the Echo virus category.

Of interest is the fact that only a proportion (unstated) of Boissard's cases excreting virus had the typical rubelliform rash. Garnett *et al.*[43] state that 25% in their series developed the rash; Rotem[122] states 18%.

Of further interest is the fact that only a proportion of the new strains retained their pathogenicity for baby mice after a passage or two in tissue culture, thus accounting for the apparent difference between the organism isolated by Tyrrell and Snell and that of Crawford.

Nottingham meningitis and at least some of its namesakes are, then, caused by Echo type 9 virus. It seems clear now that Echo viruses can be pathogenic for man, and that types 6 and 9 and possibly type 2 and others can cause aseptic meningitis. Any other clear relationship of the 14 types of Echo viruses to disease in man has not yet been established.

VIRUSES PRODUCING UPPER RESPIRATORY INFECTIONS. In a recent review of the subject, Dingle and Feller[26] point out that judging from their studies of Cleveland families, 66% of all illnesses are respiratory infections and 95% of these respiratory infections are of nonbacterial and noninfluenzal origin. Evans'[38] estimate, based on a university population, is 92%. Since the days of the Commission on Acute Respiratory Diseases started during World War II such infections have been classified, according to clinical pattern[25], as 1) Acute Respiratory Disease (A.R.D.), 2) Nonbacterial Exudative Pharyngitis, 3) Primary Atypical Pneumonia (P.A.P.), and 4) Common Cold. This division had basis beyond the purely clinical. The commission showed in work with volunteers given filtered nasal washings from typical cases that immunity to A.R.D. could be produced by prior infection and that there was no cross immunity with typical P.A.P. or the common cold. It soon became obvious, however, that such a classification based on severity of disease picture could not be expected to separate different virus infections; organisms causing mild respiratory infections in some would cause P.A.P. in others, and organisms causing primary P.A.P. in most apparently caused only mild symptoms in others in the same epidemic. This impression has been borne out in studies with some of the newly isolated etiologic agents responsible for respiratory infections. It will, therefore, be clearer to discuss respiratory infections with emphasis first on the infecting agent and then on the disease picture produced.

The Adenovirus Group. Rowe *et*

al.[126], while growing adenoid tissue in tissue cultures as host cells for certain viruses, observed cytopathic action which has been shown to be produced by a group of viruses latent in normal adenoids. These agents have been called A–D or adenoid degenerating viruses, A.P.C. or adenoidal pharyngeal conjunctival viruses and ultimately, as result of general agreement, "Adenoviruses"[34]. Hilleman and Werner[54], studying respiratory diseases in recruits, isolated in HeLa cells from throat washings of a patient with P.A.P. an agent which they called RI–67 virus and which they showed to belong to the adenovirus group (adenovirus type 4[60]). So far, 14 antigenically distinct types of adenovirus have been found, many of which are important in the study of respiratory infections. The group as a whole has a common complement fixing antigen which provides a useful screening tool, and each type within the group has an antigen which stimulates type specific neutralizing antibody.

Ginsberg *et al.*[45], using paired sera saved from the volunteer experiments carried out by the Commission on Acute Respiratory Diseases, confirmed the findings of the commission by demonstrating that an antibody rise to RI–67 or adenovirus type 4 occurred regularly in A.R.D. patients, that the antibody apparently had a protective effect against infection with the same virus, and that there was no serological crossing with sera from cases with P.A.P. or the common cold. Berge *et al.*[11] recovered adenovirus types 3, 4 and 7 from A.R.D. patients at Fort Ord, California, and it has become generally considered that these 3 types, especially types 4 and 7[52,55], are the ones found with by far the greatest frequency in recruit A.R.D. On this basis, formalin-[52,53,58,135] and heat-inactivated vaccines[58] were prepared and tested in volunteers[52,58] and recruits[52,53,135]. High levels of antibody were obtained and there was marked reduction in incidence of challenge infection in volunteers and a 98% reduction in naturally acquired disease in recruits. Infection cannot be induced regularly in volunteers by the "natural" means of swabbing throats with cultivated virus, but infection of a milder nature, conjunctivitis, pharyngitis and sometimes sore throat, cough and fever, can be induced by conjunctival swabbing with virus. Specific antibody response is elicited by this "unnatural" disease.

Evidence is good, then, that adenovirus types 3, 4 and 7 and possibly others cause A.R.D. Virus can be easily isolated from throat washings of patients with disease. Infection is regularly followed by specific antibody rise, and the antibodies, whether naturally acquired or developed as a result of vaccination, decrease incidence of reinfection. In addition, a similar though usually not identical infection can be produced in volunteers with cultivated virus. For some reason, adenoviruses are a much more frequent cause of A.R.D. in recruit populations than in seasoned military or civilian populations. This difference has not been explained[74].

Adenoviruses, especially type 3, have been repeatedly found in stools, throat washings and conjunctiva of children and adults with "pharyngeal conjunctival fever" in Washington, Virginia[60,107], Toronto[104], and Ohio[141]. Type 3 specific neutralizing antibodies and group specific complement fixing antibodies develop regularly in the course of disease. The disease picture can be reproduced in volunteers by conjunctival swabbing and its incidence can be reduced by vaccination[58]. Evidence that adenovirus type

3 is a cause of pharyngeal conjunctival fever is good.

There is also convincing evidence that adenoviruses, especially type 3, cause less well-defined respiratory infections such as "summer sore throat" and nonbacterial exudative pharyngitis. This latter entity occurs frequently in epidemic form and has been studied in some detail in family epidemics[45]. Throat cultures of 31 sick individuals planted in HeLa cells grew out 13 cytopathogenic agents. Of these 9, or 69%, were identified as adenovirus type 3, 2 were similar to adenovirus type 2 and 2 were herpes simplex virus. Of the 31 ill persons examined, 22 or 71% showed an antibody rise to one of the two adenoviruses. Sixty-one well persons from the above family groups in which at least two infections had occurred were also tested for antibody rise. Two of these well individuals did have a rise indicating asymptomatic infection, but 97% did not, suggesting that the subclinical attack rate is very low and also that the presence of the virus correlates well with the presence of pharyngitis.

It is evident that there are many causes of the "summer sore throat" syndrome. Adenoviruses probably account for many. Coxsackie A viruses account for some which occur with and without the full-blown picture of herpangina[10]. Herpes simplex virus[38,45] has been found in the course of several studies in the absence of herpetic mucous membrane lesions, but conclusive evidence of its etiologic role has not been established. Polioviruses and Coxsackie B strains have been found as infecting agents in family studies of what were thought to be respiratory infections[75].

Adenoviruses can cause primary atypical pneumonia[45], though perhaps not the variety in the course of which cold agglutinins and streptococcus MG agglutinins develop. The original RI–67 agent or adenovirus type 4 was isolated from a patient with the clinical pattern of P.A.P., and patients serologically diagnosed as having A.R.D. during A.R.D. epidemics have developed pneumonia. Most P.A.P. patients, however, do not develop antibodies to adenoviruses, regardless of whether their illness is associated with a rise in titer of cold agglutinins.

Primary Atypical Pneumonia Virus (Eaton). As early as 1944, an agent was isolated by Eaton *et al.*[29] from P.A.P. patients of the cold agglutinin and streptococcus MG agglutinin-developing type. Recent work by Liu, Eaton and Heyl with the same virus[30] is strengthening its identity as a causative agent of this variety of the disease. Antibody in convalescent serum from patients is specifically taken up by chick embryo-grown Eaton virus as shown by the fluorescent antibody technique. The same method can be used to titrate the rising antibody level in the serum of P.A.P. cases. Recently, the same workers have isolated 4 new strains, 3 from sputum of patients in the acute stage of illness and one from the lung of a fatal case. All react with human convalescent serum and not with acute phase serum, all give pneumonia in cotton rats which can be neutralized by convalescent human serum, and all cross react antigenically with each other and with the 1944 strain. In patients recovered from P.A.P. infection, antibody appeared between the 2nd and 3rd week of illness. Of 44 patients' sera collected in the Boston area, about 70% showed antibody to P.A.P. virus. Of 27 cases from a boy's school epidemic of P.A.P., 100% developed antibody and most of these had cold agglutinins. There was no crossing with adenoviruses, or the causative agents of influenza, psittacosis or Q fever. The evidence suggests

that the Eaton virus is one of the etiologic agents of P.A.P. It is evident, however, that P.A.P. as currently diagnosed is a syndrome of multiple etiology.

Arakawa *et al.*[8] have isolated a virus from serum and pleural fluid of P.A.P. patients by intracerebral passage through mice and chorioallantoic passage in eggs. The virus is neutralized by convalescent serum and is said to produce pneumonia in monkeys. The status of its relationship to Eaton virus and to P.A.P. is not clear.

Common Cold Virus. This topic has been reviewed recently by Gohd[46] and will not be covered here in the absence of new developments since that review. While a common cold virus can, perhaps, be grown in tissue culture[6], there are no cytopathic changes and volunteers are still required for identification. Current studies of a histiocyte count change in eggs infected with an egg adapted virus are not sufficiently developed for comment at this time.

Newborn Virus Pneumonitis (Type Sendai). Between March and May, 1952, in Sendai, Japan[129] there was a severe outbreak of pneumonitis in a newborn nursery resulting in death of 11 of the 17 babies affected. Ages of the sick infants ranged from one to 21 days. The onset was very abrupt, with fever, dyspnea, and cyanosis, and in 8 "pronounced jaundice." Physical findings were minimal until just before death, but roentgenograms of the chest showed marked changes with diffuse shadows in one or both lungs and "definite branch-like shadows" bilaterally in some. Temperature curves were spiking with wide swings, death usually occurring at the height of a swing.

There were 9 necropsies[102], all of which showed intensely hyperemic lungs with irregular nidi of hemorrhagic pneumonia bilaterally and infiltration of alveolar septa with mononuclear cells and "oblong cells with vesicular nuclei." No inclusions were seen in any cells in the lungs or pharynx. There was no hyaline membrane. Livers showed "macular turbidity" and "serous hepatitis with conspicuous overgrowth of Kupffer's cells accompanying central fatty degeneration." There was leptomeningitis but no encephalitis. There were hemorrhagic spots on the serous membranes throughout the body including the pericardium, and hemorrhagic erosions were found in the stomach mucosa in the majority of the necropsies.

Kuroya *et al.*[86] isolated agents from all 5 of the infant lungs studied by inoculating mice intranasally with lung suspension. The virus produced mouse lung changes similar to those of influenza virus. The new virus was not neutralized by antisera to influenza A, A^1, B or C, however, or by mumps or N.D.V. antisera. It was neutralized by serum of recovered infants, the serum of a patient's mother who had had a respiratory illness, and serum of rabbits who had been immunized with the new virus. Later, a new strain was isolated from throat washings of a surviving patient, and paired sera were obtained which showed a rising antibody titer. Further, an 8-year-old volunteer was given a suspension of infected mouse lung by the "peribronchial route." She developed a biphasic temperature curve with increased lung shadows on roentgenogram but her illness was much milder than that of the infants. Virus was isolated from her throat on the 3rd and 7th day, and a clear antibody titer rise to the new virus was shown without accompanying rise in titer to influenza A, A^1 or B. A sketchy serological survey done at that time showed antibody in the population of Sendai but rarely elsewhere in Japan. A sub-

sequent report[81] showed that by 1954 antibody could be found throughout the country, but with higher titers in endemic areas like Sendai.

Jensen *et al.*[68] in this country have confirmed the fact that the virus is distinct from influenza A, A^1, B and C, and from all other known viruses of mouse and human origin that are in any way similar to this new one. Because of its influenza-like characteristics they suggest it be called "influenza D." In a survey of sera collected from various parts of the United States they found that 40% of all samples tested had a titer of 1/32 or more. Two of their sets of paired sera showed distinct antibody rises in the convalescent serum to "influenza D" without rises in other influenza antibody titers. One case had been diagnosed "primary atypical pneumonia" and the other, "mild respiratory illness." Six individuals from whom serum had been obtained at intervals showed antibody titer increases between two samples, and two of these were close enough together to show that the rise occurred between September, 1952, and March, 1953, and between September, 1952, and January, 1953. No serum collected from children of 6 months to 3 years contained antibody. The highest titers were found in those of 10 to 13 years. No report could be found of isolation of the virus in the United States.

Recently, two papers report the finding of serological evidence of Sendai Virus infection in Great Britain[48,150]. In both studies, serological investigations of influenza or pneumonia were being carried out and a few examples of clear-cut antibody rise to Sendai virus were found, both with and without simultaneous rise in titer to other influenza viruses. In the paper of Grist *et al.*[48], adults admitted to the hospital pneumonia ward and 6 adults treated in their homes for influenza had clear-cut rise in antibody titer to Sendai virus. In the report of White *et al.*[150], of an influenza outbreak in a town and nearby hospital for the chronically sick, only 34% of the hospital patients developed antibodies to influenza A, the current epidemic strain. Consequently, the remaining 66% of the sera were tested for antibodies to other viruses. Five serum pairs showed clear-cut rising titers to Sendai virus and 2 had high titers in both samples. In addition, a technician who bled one of the patients had a mild respiratory illness in the course of which he developed antibodies to Sendai virus only. In both studies the influenza D cases occurred during outbreaks due to more usual varieties of influenza infection.

In summary, a new virus which may be called "influenza D" instead of the current "newborn pneumonitis virus, type Sendai" has been shown to cause a severe and frequently fatal pneumonitis in the newborn and a moderately severe pneumonia in the one older child to whom it was given by inoculation. Serologic studies show that it is present in the population in this country, and that infection with it was concurrent with, and may have caused, a case of primary atypical pneumonia and a mild respiratory illness. It has apparently been associated with pneumonia and with an influenza-like picture in Great Britain. Since it is easy to isolate and identify, it will probably be found when searched for.

Canine Distemper Virus. For years there has been intermittent interest in the idea that canine distemper virus can cause infection in man. This interest has been rejuvenated by Adams' comparison[2] of the pathological pictures in animals with distemper and humans with primary pneumonitis, and particularly by his presentation of two

cases of children with pneumonitis who developed antibodies to distemper virus in the course of illness. One child developed his illness 10 days following the death of his puppy from distemper. The other child developed pneumonitis in the course of a small institutional epidemic of acute respiratory disease. Adams[7] and others have shown the presence of antibodies to distemper virus in human gamma globulin. Karzon[76] has extended this to show that neutralizing antibodies to the virus were widespread in the Buffalo population, and that they were transmitted transplacentally to the infant, were lost by the 6th month, and reappeared between the 2nd and 10th years of life. Almost 100% of adults in the Buffalo area had antibody to distemper virus in their serum. Carlström[15] using a different type of neutralization test, found a very similar serum antibody distribution in Sweden.

While the evidence is good that C.D.V. or a closely related virus does infect man, its connection with disease, if any, is still unknown. Adams' observations have not yet been confirmed and no reports have been found of the isolation of the virus from man.

Giant Cell Pneumonia. Enders[31] makes brief mention in a published lecture of the isolation of a virus closely resembling measles virus from the lung tissue of one patient and from the tracheal secretions of another dying of giant cell pneumonia. Convalescent phase measles serum neutralizes this giant cell pneumonia virus, and cross neutralization and cross complement fixation tests using measles and new virus immune monkey serum suggest that the two viruses are the same or closely related. If they are shown to be the same, it is still unknown whether this represents initial infection with measles virus without rash, or activation of latent measles virus in one who was previously infected, or whether the virus is connected with the disease at all. The situation is interesting regardless of its outcome.

Lest the foregoing section leave the impression that it is now possible to define the etiology of respiratory diseases in most patients, it is well to note that despite the accomplishments in this field, by far the majority of cases remain undiagnosed even when an active laboratory is available. Evans' results in his study of 290 Wisconsin students[38] with upper respiratory infections show that only 16.7% could be diagnosed: 8.3% were streptococcal tonsillitis and pharyngitis, 3.4% were of influenza virus origin, 1.3% were "herpetic infections," 1.6% were bacterial pneumonia, 0.3% were psittacosis and only 2% were adenovirus infections. Jordan quotes 2% incidence of respiratory disease due to adenovirus from the Cleveland family studies[75], and Price[111], 4%.

No study has been found so far in which a systematic attempt was made to identify by isolation or serologic methods the role of all the currently suspected causes of respiratory infection. Except in the course of epidemics, the proportion of cases in which etiology can be defined would probably still be small.

MISCELLANEOUS DISEASE ENTITIES. 1. *Cytomegalic Inclusion Disease.* Various observers[39,92] have noted large cells with intranuclear inclusions in the salivary glands in about 10 to 30% of routine necropsies. In about 1% of infants and young children these cells are found generally distributed throughout the body and the diagnosis of cytomegalic inclusion disease may be made[152].

Recently, Rowe *et al.*, in Bethesda[125], Smith, in St. Louis[133], and Weller *et al.*, in Boston[145], independently and using different methods, isolated a new cyto-

pathogenic agent in tissue culture which produced changes in cells similar to those found in nature. Rowe *et al.* found focal areas of spontaneous degeneration in the fibroblastic outgrowth of "normal" adenoid tissue obtained from 3 children. The areas were distinct from those formed by adenoviruses and were shown to consist of rounded or oval cells containing large eosinophilic intranuclear inclusions with margination of chromatin and halo formation. Only fibroblasts were involved.

Smith removed both submaxillary salivary glands at necropsy, froze one and sectioned the other. Her first strain of virus was isolated by inoculating inclusion containing gland tissue from a 7-month-old child dying from an adrenal carcinoma into cultures of human uterus tissue. Her second agent was isolated in similar manner from the kidney of a 1-month-old child who died of cytomegalic inclusion disease. In both instances, growth characteristics and appearance of cytopathic changes were similar to those described for Rowe's strains.

Weller used human foreskin and human embryo skin muscle tissue cultures and studied material from three typical cases of generalized cytomegalic inclusion disease. A similar type virus grew out in fibroblastic tissue inoculated with liver biopsy material from one case, urine and liver biopsy from another, and with urine from a third case.

Each laboratory carried out neutralization or complement fixation tests for antibody against their strains of the virus, but in no instance was sufficient reproducible work carried out in patients with demonstrable disease for the tests to be considered as giving more than suggestive results.

Rowe compared virus strains from the three laboratories and found that all had similar cytopathic changes, growth characteristics, and the like, and all behaved identically serologically. As well as can be determined at this stage, the various strains isolated by different means from the different areas are the same or closely related. It seems likely that these viruses are the cause of cytomegalic inclusion disease but available serological techniques are still open to question as definitive diagnostic tools.

2. *Croup.* Croup has long been thought to be a disease of diverse etiology, with at least some of the cases due to virus infection[112]. Recently, two groups of independent observers have isolated very similar viruses from cases of croup in Toronto[97] and Cincinnati[16]. From 21 severe cases in which Morgan *et al.*[97] studied tracheal secretions, two new agents were isolated in human embryo lung and monkey kidney tissue. These two were capable of serial passage in monkey kidney cells. Three additional agents caused similar changes in both types of cells, but the change could not be transmitted. More recently, Beale *et al.*[9], using HeLa and human amnion cells, isolated cytopathogenic agents from 10 of 15 cases. Chanock, in Cincinnati, isolated two similar viruses from throat swabs of 12 cases using monkey kidney cells. Five of 11 of these cases developed antibody in their sera. One of 16 control infants with nonrespiratory illness developed antibody. Chanock made a careful study of the characteristics of this new agent which he called "croup associated" or C.A. virus, and found it to be quite similar to the influenza-mumps-N.D.V. group of viruses, and to the newborn pneumonitis virus (type Sendai). No significant antigenic relationship was found, however, between any of these and the new C.A. viruses. Chanock studied a strain obtained from Beale

(Toronto), and was unable to detect a difference from the Cincinnati strains in growth characteristics, hemagglutination or antigenicity.

Several strains of a very similar or identical virus have been isolated from croup patients in different laboratories by different methods. Patients developed antibody to the virus in the course of illness. This suggests that the agent is perhaps one of the causes of croup syndrome.

3. *Myocarditis.* Recently, in papers from South Africa[63], Boston[80], and The Netherlands[140,142], Coxsackie Group B viruses have been incriminated as causative agents in severe generalized infections in the newborn with a high morbidity and mortality rate. Onset of disease was usually very sudden and in many instances babies died within a few hours of onset with fever, tachycardia, cyanosis and final circulatory collapse. In many cases, but not all, there was a brief nonspecific febrile illness lasting a few days with a remission before onset of the acute fulminating phase. At postmortem the babies had, among other changes, myocarditis and early encephalitis. Virus has been isolated from brain tissue 3 times[14,140,142], from thoracic cord once[80], from the myocardium at least 6 times[63,80,140,142], and from stools three times[96]. The mother of the Boston baby, whose infection was apparently transmitted through the placenta, developed neutralizing antibodies to the infecting strain. She had had only a mild upper respiratory infection 2 days before delivery (by cesarean section).

The isolation of Coxsackie B viruses (so far, types 3 and 4) from internal organs of babies dying of similar disease in Boston, Africa and The Netherlands makes the evidence in favor of these agents as cause of disease fairly conclusive.

Hepatitis Virus. Most of the current knowledge of infectious hepatitis virus derives from work done in volunteers. Efforts have been made to isolate the virus in tissue culture, but consistent, convincing results have not yet been obtained. Recently, Rightsel *et al.*[117] have reported development of cytopathic changes in Detroit 6 epithelial cell cultures from icteric serum and from stools of cases of infectious hepatitis. The changes seem to consist solely of clumping of a proportion of the cells exposed, but in their hands these changes have been consistently transmissible in further passages in the same cell system. The cytopathic effect described sounds indefinite and must await further exploration before evaluation.

BRIEF SUMMARIES OF TWO OF THE NEW VIRUS GROUPS. In the interest of completeness and in order to counteract the impression that the organization of this article according to disease picture may have produced, two new virus groups, the adenoviruses and the Coxsackie viruses, each of which includes a large number of different types, will be very briefly discussed.

Adenoviruses. There are at least 14 different types of adenoviruses which have been isolated to date, 12 of human and 2 of simian origin[124]. (Rowe now refers to 16, details not yet published[123]). A few have been extensively studied in relation to disease (see section on respiratory infections), and others are rarely found or their relation to disease is still uncertain.

The most frequently found adenoviruses are types 1 through 7. Types 1, 2, 5 and 6 are those most frequently grown out as latent viruses from "normal" adenoid and tonsil tissue[58,127], 91% of them being types 1, 2 and 5[123]. (Schlesinger[131] reports that 70 to 80% of the tonsils and adenoids grown in tissue culture yielded latent virus,

usually types 1 and 2.) Types 1, 2 and 5 have been found repeatedly in very early age groups in association with mild febrile respiratory infections. Eighty-one per cent of the isolates are from those under 4 years of age, and 12% additional from those from 4 to 10 years of age[123].

Type 3 has been shown to cause pharyngeal conjunctival fever, simple conjunctivitis[123], nonbacterial exudative pharyngitis and A.R.D. It has been found by Neva and Enders in association with a case of roseola infantum, and has been grown from the lung and mesenteric lymph nodes of a child with Letterer-Siwe disease[60]. Kjellen has isolated an unidentified type (type 3?) from the stools of 3 patients with mesenteric-adenitis and from a mesenteric lymph node of one[84].

Types 4 and 7 have been frequently associated with A.R.D. Types 6[123] and 10[123,124] have been isolated from the eyes of patients with conjunctivitis. Type 8[65,66] has been isolated once, by Jawetz *et al.*, from a typical case of epidemic keratoconjunctivitis (E.K.C.). Using their type 8 strain they have demonstrated a high incidence of neutralizing antibodies in the convalescent sera of E.K.C. patients collected from Japan, Italy, Switzerland and North America and an absence of these antibodies in almost all sera collected from these areas from individuals with a negative history for E.K.C. Paired sera from cases show a rising titer to type 8. (In addition, Jawetz reported transmission of typical disease to volunteers using cultivated virus[64].) This constant association of virus with disease is highly suggestive of cause and effect. Only one strain has been isolated to date, however, and this work has not yet been confirmed.

Even less is known about the remaining types, most of which have been isolated from stools on a single occasion.

Coxsackie Viruses. Coxsackie viruses have been reviewed recently by Dalldorf[22], and a good proportion of the more recent work has been included in this paper in the sections on Aseptic Meningitis and Myocarditis.

Coxsackie viruses are divided into two groups, A and B, on the basis of their pathologic behavior in suckling mice. There are at least 19 antigenic types within Group A, only 5 (7[115]) of which are cytopathogenic in tissue culture, and 5 types in Group B, all of which are cytopathogenic. Group A viruses have been found generally distributed in the stools of clinically healthy individuals[56,106] (1.5 to 7.5%)[105], and in association with other viruses such as herpes simplex and polio, so that unusually good evidence is required to identify them definitely as causes of disease. So far the evidence indicates that Group A, types 2, 4, 5, 6, 8 and 10 may cause herpangina. The evidence for this statement consists 1) of multiple isolations of virus from stools and throat washings from many areas[59,85,143], 2) of demonstration of regular rise in antibody titer to strains isolated, 3) of epidemiological studies including family studies in which, coincident with the development of an epidemic, the virus appeared in an area which had been free of it, and 4) of history of close contact between cases[59].

Since herpangina can apparently occur without typical pharyngeal lesions as judged by family studies[10], it can be considered as a cause of summer sore throat and nonspecific pharyngitis. Group A, type 2 has been found in throat washings and stools of cases with an entity called "three-day fever," which consists of fever, headache and pharyngitis with or without throat vesicles[143]. Specific neutralizing

antibodies developed. It is difficult to distinguish such disease entities from herpangina, however, and they are all probably variants of the same disease picture.

Coxsackie A9 has been found frequently in association with aseptic meningitis, but has not yet been isolated from spinal fluid.

In summary, Group A Coxsackie viruses cause herpangina and herpangina-like syndromes, but are not yet definitely known to cause other disease entities.

Group B Coxsackie viruses, on the other hand, are rarely found in normal individuals and apparently cause a wide variety of clinical pictures, especially those which include symptoms of meningeal and muscle involvement. Group B viruses have been established as a cause of aseptic meningitis, as discussed before, and of Bornholm disease or pleurodynia on the basis of constant association of virus with disease in different areas and in careful epidemiological and family studies[69,70]. Johnsson[70] and Gard[41] point out the association between aseptic meningitis and pleurodynia in Sweden, aseptic meningitis occurring in the younger age groups and pleurodynia in the adult family contacts.

Many of the disease pictures associated with Group B viruses include the symptom of myalgia in varying degree, and in at least two instances myalgia has been the only prominent symptom[89]. In both there was severe localized muscle pain, and biopsy at the point of maximum tenderness showed muscle with degenerative and inflammatory changes. Virus was isolated from both biopsy tissues and from the stools of both cases.

There are many scattered reports connecting a vague infectious mononucleosis-like syndrome with the finding of Coxsackie B viruses[57,82,118]. These disease pictures may or may not include splenomegaly and lymphadenopathy, but do include the production of up to 11% "atypical lymphocytes" in the peripheral blood with negative heterophile agglutinin tests. The atypical lymphs may occur in association with the more typical Coxsackie B picture of myalgia, headache, and others, strengthening the possible relationships between virus and blood change. There is still just suggestive evidence on this point, but similar reports from different parts of the world make the suggestion worthy of note.

It is also worth noting that complications of Coxsackie B infections are so varied that when they are the predominant finding, diagnosis of an isolated case can be very difficult. Coxsackie infection, in one brief epidemic, has been called infectious mononucleosis, appendicitis, sinusitis, pleurodynia and influenza before it was identified[82]. In other studies, the variation has been as marked[57,134]. Orchitis has frequently been mentioned as a complication of pleurodynia and can be especially confusing when other symptoms are of "minor illness" nature.

In summary, then, Coxsackie Group A viruses are frequently found in nature not associated with disease but may cause herpangina and mild pharyngitis. Coxsackie Group B viruses are rarely found in nature unassociated with disease and cause illnesses of wide variety. The illnesses usually have a common basis, however, in producing symptoms of meningeal and muscle involvement.

It should be clear from the foregoing that many new viruses are being isolated about which relatively little is known, including their etiologic relationship to the disease entity in the course of which they were found. It should also be clear that most of the

disease entities discussed are syndromes of multiple etiology and that the clinician is entirely dependent on the laboratory to establish the etiology in any given case. Since the solution and the study of new viruses is so far outdistancing the development of diagnostic facilities available to the clinician, it is perhaps just as well that so little is known in the way of specific therapy for any specific type of disease discussed above.

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GYNECOLOGY AND OBSTETRICS

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ANTIHYPERTENSIVE DRUG THERAPY IN THE MANAGEMENT OF TOXEMIA OF PREGNANCY

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CIRCULATORY DYNAMICS OF PREGNANCY. Although the basic etiology of toxemia of pregnancy remains an enigma, the presence of generalized arteriolar vasoconstriction has long been recognized. The usual circulatory changes that occur in pregnancy include an increase in heart rate, beginning early in pregnancy and rising to a maximum at the eighth month, with slowing in the last few weeks to about ten beats per minute above the pregestational level. In association with tachycardia is an increase in oxygen consumption, presumably related to metabolism of the fetus and uterus. There is an increase in cardiac output of 40 to 50%, which reaches a maximum at the eighth month, returning toward normal in the last weeks of pregnancy. The blood volume rises to a peak in the seventh to eighth month and diminishes as term approaches. The blood pressure may be unchanged or there may be a fall in diastolic pressure and rise in pulse pressure. Burwell[6] has recently reviewed these hemodynamic changes.

These factors give evidence of the circulatory burden, and suggest that if careful control of the patient with cardiovascular disease is exercised at the time of the maximum load in the seventh or eighth month, cardiac symptoms may then improve in the final weeks of pregnancy. At the time of delivery there may be a sudden increase in peripheral resistance due to closure or obliteration of the placental "arteriovenous shunt"[17]; this presents a threat of postpartum congestive failure due to increased fluid absorption from the tissues into the vascular compartment.

INFLUENCE OF PLACENTAL STEROIDS ON BLOOD PRESSURE. The normal level of blood pressure during pregnancy is maintained by an interplay of homeostatic mechanisms involving increased heart rate, blood volume, and cardiac output. Homeostasis may be further influenced by placental corticoid formation, including aldosterone, which reaches a peak concentration in the

third trimester. Raab[30] believes that toxemic hypertension is due to an increased formation of sodium-retaining corticoids (such as aldosterone) and their effects on arteriolar vascular contractility. These presumably sensitize the vessels to the intrinsic sympathetic and humoral pressor catechol amines. They may contribute also to the development of edema and albuminuria. The observed augmentation of renal vascular resistance that occurs in toxemia of pregnancy may similarly be attributable to corticoid-induced sensitization of the renal vessels to constrictor catechol amines. Furthermore, increased sensitivity of the cerebral vessels may be a major factor in determining the degree of increase in cerebral vascular resistance seen in toxemia[25,30].

In addition to acting directly upon blood vessels, it is suggested that the circulating humoral agent of toxemia may produce vasoconstriction through a central effect on the sympathetic nervous system[24]. The central blockade of sympathetic vasoconstrictor impulses forms the empiric basis for the current use of antihypertensive drugs in toxemia.

BLOOD PRESSURE CHANGES DURING PREGNANCY. The relationship between essential hypertension and toxemic hypertension remains obscure. It has been suggested[4] that the development of chronic hypertension following toxemia is not a result of the pre-eclamptic toxemia, but rather an unmasking of a tendency toward hypertension, allowing it to develop earlier than it otherwise would have done. Women with essential hypertension appear more likely to develop toxemia than are those with normal blood pressure[14,21]. In addition, toxemia may be followed by acceleration in the course of a patient's cardiovascular disease[21].

The course of essential hypertension during pregnancy is such that about one-third of the patients may be expected to undergo a fall in blood pressure to normotensive levels, one-third to remain at their usual hypertensive level throughout pregnancy, and one-third to have a rise, possibly developing their highest blood pressures in the last week of pregnancy, at delivery, or immediately postpartum[15].

ESSENTIAL HYPERTENSION VERSUS TOXEMIA. It is important to attempt to distinguish between toxemia, essential hypertension, and essential hypertension with superimposed toxemia in relation to management and prognosis. Certainly some women who are hypertensive, but show little evidence of vascular damage, may present no problem during their pregnancies. On the other hand, those who show toxemia engrafted upon severe hypertensive vascular disease may be more difficult to treat, since the blood pressures are usually higher than in the true toxemic group and the superimposed toxemia may be more severe. Although signs of toxemia most frequently develop in the eighth or ninth month of pregnancy in the group with true toxemia, they may develop in the fourth or fifth month in those with hypertension and superimposed toxemia; the earlier in pregnancy they develop, the greater the fetal mortality rate[15].

Patients with toxemia usually present no abnormalities until after the twenty-fourth week of pregnancy, when a rise in blood pressure is first noted. The diastolic rise may be greater than the systolic. Subsequently edema and albuminuria may appear. It is helpful to realize that the hypertension of toxemia does not depend upon the attainment of a specific height of blood pressure. Rather, we should be impressed with the relative rise in diastolic pressure which, although it may

be only 20 mm. Hg, may be of clinical importance. It is difficult to overcome, in the evaluation of obstetrical patients, fixed ideas concerning the normal range of diastolic blood pressures.

FUNDUSCOPIC CHANGES. The retinal fundi in toxemia are usually normal except for occasional segmental vasospasm. In acute eclampsia one may see hemorrhages and exudates. Finnerty[15] has called attention to a generalized retinal sheen which he attributes to superficial retinal edema, a possible consequence of the generalized vasospasm characteristic of toxemia. This is said not to occur in hypertensive vascular disease. He has noted retinal sheen in toxemia as long as 4 weeks before elevation of the blood pressure, edema, and albuminuria appear. Thus it may be a useful sign of impending danger; likewise its persistence in spite of only mild hypertension may warn against a false feeling of security.

It remains to be proved that toxemia, appearing for the first time in a previously normotensive patient, can produce permanent vascular damage. It is sometimes difficult to distinguish between toxemia and hypertensive vascular disease. In addition, some patients may have been hypertensive, only to have their blood pressures fall to normal during pregnancy. Their return to hypertensive levels in the postpartum period might be misinterpreted as a sequel to toxemia. The incidence of hypertensive and permanent vascular damage after toxemia seems to be related more to the duration of the toxemia than to its severity[7]. Accordingly there has been observed a greater incidence of permanent vascular damage following toxemia without convulsions than after frank eclampsia[11,28]. Although convulsive toxemia of pregnancy is now seen infrequently, hypertension associated with pregnancy and nonconvulsive toxemia continue to present problems in care of the patient.

CLINICAL APPROACH. It has been our policy to admit to the hospital patients who are discovered to have toxemia of pregnancy or hypertension associated with pregnancy. At that time we perform laboratory studies which may be helpful in evaluating the extent of the vascular damage to the heart, eyes, and kidneys. These tests include urinalysis, quantitative urine protein measurement, blood urea nitrogen, uric acid, intravenous phenolsulfonphthalein excretion test, funduscopy, electrocardiography, and orthodiagraphy. Daily blood pressures obtained at this time are often helpful in the evaluation of future trends. Urinary output and daily weight determinations are important with respect to fluid exchange.

Spectrum of Treatment. GENERAL MEASURES. Much of the credit for a decreasing incidence of toxemia may be attributed to improved prenatal care. Certainly many patients will respond to measures such as bed rest, sedation, sodium restriction to less than one gram per day, and avoidance of excessive weight gain. Strict fluid restriction usually is not necessary if the daily output is replaced and about 600 ml. per day added, to make up for the insensible loss of fluid. Diamox and mercurial diuretics can be used if fluid retention is excessive.

SEDATION AND MAGNESIUM SULFATE. Prior to the availability of specific antihypertensive drugs, treatment of toxemia in the hospitalized patient included the use of massive sedation and magnesium sulfate. Large doses of morphine sulfate, chloral hydrate, phenobarbital, or paraldehyde were of limited value in controlling hypertension, and offered the danger of marked respiratory depression of both mother and fetus.

More recently chlorpromazine, which does not depress fetal respiration, has

been used to potentiate the sedative effect of phenobarbital, thereby reducing the dosage of the sedative and diminishing the depressant effect on the fetus. Magnesium sulfate has been used in doses of 10 ml. of a 50% solution intramuscularly, either alone or in combination with other sedative agents. Magnesium produces a true depression of the central nervous system, the vital medullary centers being particularly vulnerable, so that the danger of respiratory depression is great. A solution of 10% calcium gluconate should be available as the antidote. The trend is toward the use of more specific hypotensive drugs to replace magnesium sulfate and massive sedation.

Newer Antihypertensive Drugs. The advent of new, safe and effective hypotensive drugs offers possibilities for reducing the fetal mortality in toxemia of pregnancy. However, hypotensive drugs should supplement rather than replace good medical and obstetrical treatment. Depressor therapy must be adapted to the individual with highly potent drugs reserved for those in real danger. Patients with mild hypertension often can be managed at home with bed rest and mild sedation.

It is possible to classify newer agents into three groups according to their sites of action. A knowledge of drug action, side effects, toxicity, comparative potency, and indications and contraindications is obligatory if they are to be used safely and successfully[32].

Adrenergic Blocking

Phentolamine (Regitine)
Benzodioxane
Phenoxybenzamine (Dibenzyline)

Ganglionic Blocking

Hexamethonium
Pentolinium (Ansolysen)
Chlorisondamine (Ecolid)
Mecamylamine (Inversine)

Centrally Blocking

Veratrum
Protoveratrine
Hydralazine (Apresoline)
Reserpine

ADRENERGIC BLOCKING DRUGS. Regitine and benzodioxane are effective in blocking the pressor effect of circulating epinephrine and norepinephrine. Since these catechol amines apparently do not participate in the hypertension of toxemia[23], they have been used primarily for the diagnosis of the adrenal medullary tumor, pheochromocytoma. Phenoxybenzamine (Dibenzyline) blocks sympathetic impulses traveling to the blood vessels at the peripheral effector site. Its effectiveness is limited by its production of severe postural hypotension, orthostatic tachycardia, and nasal stuffiness[32]. So, it is of little value in the management of toxemia.

GANGLIONIC BLOCKING DRUGS. These drugs act at the level of the spinal autonomic ganglia to block neurogenic vasoconstrictor impulses. The accompanying parasympathetic blockade results in constipation which may progress to paralytic ileus, impairment of visual accommodation, and dryness of the mouth. These are probably the most potent and potentially the most dangerous antihypertensive agents now available. In the management of toxemia, Ashe[1] encountered intrauterine death in 3 of 4 patients who developed severe hypotension and syncope. He subsequently discontinued the use of hexamethonium for this reason. All ganglionic blocking drugs are capable of producing similar severe hypotension with resultant decrease in uterine blood flow, fetal anoxia, and death of the fetus. Therefore, in spite of recent refinements in these drugs, such as the rapid absorption provided by mecamylamine (Inversine), we do not feel that there is a place for ganglionic

blocking drugs in the treatment of toxemia of pregnancy.

CENTRALLY BLOCKING DRUGS. These agents, which include veratrum viride and veratrum album alkaloids, hydralazine, and the Rauwolfia alkaloids, have been found to be the most effective drugs for reducing the hypertension of toxemia.

Veratrum. Although veratrum viride was used in the treatment of toxemia as early as 1859, and subsequently purified alkaloids have been prepared, these substances still fall short of being ideal therapeutic agents. They have both a hypotensive and a cardiac slowing effect. The former is reflex in nature (von Bezold reflex). The afferent arc consists of vagal fibers arising mainly in the left ventricle leading to the central vasoconstrictor center[18]. The efferent pathway, which results in vasodilatation, has not yet been delineated. The bradycardia is also reflex in origin. It is mediated by cardiac and pulmonary vagal fibers. It can be abolished by atropine without diminishing the hypotensive action[18].

Treatment of hypertension of moderate severity, early in pregnancy, can be begun with outpatients by giving them one tablet (1 mg. or 1 unit) of Veriloid, Vergitryl, Veratrite, or Unitensen four times daily, and then increasing the dose by one tablet daily each week until an effective dose is reached. The usefulness of veratrum is limited because a full therapeutic dose is likely to produce side effects of nausea, vomiting, and salivation.

For more severe hypertension, as encountered late in pregnancy, the hospitalized patient may be treated with one of the above alkaloids of veratrum by the intravenous or intramuscular route. The average dosage of Veriloid is 0.1 to 0.3 mg. intravenously, and 0.4 to 0.6 intramuscularly. The initial hypotensive effect occurs within 8 to 15 minutes after intravenous administration; in 20 to 30 minutes when given intramuscularly. Finnerty[16] found the incidence of vomiting after intravenous veratrum to be 65 to 75%, but in over 1000 cases treated with intramuscular veratrum vomiting occurred in only 16%. He found the addition of reserpine as "background therapy" for intramuscular veratrum resulted in reduction of the incidence of vomiting to only 5%, and a prolongation of the duration of hypotension from an average of 3.5 to 8.5 hours[13].

Protoveratrine. This preparation, a mixture of pure crystalline protoveratrine A and B from veratrum album, has increased potency; but it, too is of limited usefulness because of a narrow toxic to therapeutic ratio. Protoveratrine produces a generalized decrease in arteriolar vasoconstriction which results in a fall in the cerebral and renal vascular resistance[10,27]. Meilman[26] has used subcutaneous protoveratrine in a dose of 4 to 6 μg. per kg. of body weight, repeating the effective dose at 8- to 12-hour intervals as needed. Great care should be exercised in the use of the intravenous route, since overdosage results in severe postural hypotension[26]. If the patient has been digitalized, he may experience nausea, bradycardia, and cardiac arrhythmias[20]. The latter two can be alleviated by the use of 1 mg. of atropine subcutaneously. Marked hypotension can be combated by vasopressor substances such as ephedrine or Neosynephrine. For patients with mild or moderate hypertension, protoveratrine (Veralba or Provell Maleate) can be given orally in a dose of 0.2 mg. four times daily. Each week thereafter the dose can be increased by 0.2 mg. to an average maintenance dose of 0.6 to 1.0 mg. four times daily.

Hydralazine (Apresoline). Acting as a central sympathetic antagonist,

Apresoline causes vasodilatation by reducing the outflow of sympathetic vasopressor impulses. It also neutralizes humoral pressor substances such as cerebrotonin, hypertensin, serotonin, and pherentasin[19]. It produces an increase in cerebral blood flow and cerebral oxygen consumption, and a decrease in cerebral vascular resistance[25]. Renal blood flow is increased and, associated with tachycardia, there is a rise in the cardiac output[3]. The latter two effects may be detrimental to patients with coronary artery disease[22]. In addition, tachycardia can sometimes be noted in the fetus, suggesting passage of Apresoline through the placental barrier[9]. Tachycardia can be minimized by adding reserpine to the regimen.

Using Apresoline, Finnerty[14] has achieved encouraging results in the treatment of 36 of 91 pregnant patients who appeared to have either toxemia or hypertension. The dose ranged from 200 to 400 mg. a day. For the first week of treatment a dose of 10 mg. four times daily is recommended in order to lessen the initial annoying side effects, namely headache, nausea, palpitation, flushing of the face, and nasal congestion. It is then increased each week by increments of 2 mg. four times daily to a dose not exceeding 100 mg. four times daily. The therapeutic effect of the drug is usually not enhanced by increasing the dosage beyond this. The syndrome of Apresoline toxicity characterized by arthralgia or arthritis, and a clinical picture of disseminated lupus erythematosus, occurs in an occasional patient receiving large doses (over 400 mg. daily) for long periods of time[12,29]. Short term therapy in smaller dosage during pregnancy should preclude this complication.

Intravenous Apresoline represents a very potent agent for lowering blood pressure in the severely toxemic or eclamptic patient. Assali[2] noted the onset of the hypotensive effect to be 10 to 15 minutes, the maximum effect 30 minutes, and the duration of action to range from 4 to 22 hours. The fall in diastolic blood pressure is greater than the systolic and occurs first; tachycardia is not proportional to the degree of fall in blood pressure[2]. The vasodilatation caused by Apresoline may produce a throbbing of the head with a feeling of fullness and warmth. Fall in renal[3] and cerebral[25] vascular resistance results in improved blood flow to these vital organs. Thus Apresoline seems to fulfill many of the requirements of a good antihypertensive agent for the treatment of toxemia. It may be administered intravenously by single injection in a dose of 10 to 20 mg., or by continuous infusion in a dose of 30 to 40 mg. Norepinephrine may be used to counteract an excessive hypotensive effect. A sudden precipitous fall in blood pressure does not occur as commonly as with intravenous veriloid.

Rauwolfia serpentina and reserpine. Since the introduction of *Rauwolfia serpentina* in this country by Wilkins[35,36], it has been used extensively for the treatment of hypertension. Acting presumably at the hypothalamic level, it has both sedative and vasodepressor effects. The alkaloid reserpine is thought to be the active principle. Following daily oral administration, the onset of blood pressure lowering effect does not occur for 4 to 7 days; the maximum effect appears after 3 to 4 weeks. Mild hypertension uncomplicated by toxemia can be treated by a dose of 0.25 mg. twice daily. More severe hypertension can sometimes be controlled by starting reserpine in a priming dose of 1 mg. four times daily, decreasing this dose gradually over a one-week period of

time to a maintenance level of 0.25 mg. twice daily[32].

Intravenous or intramuscular reserpine has been found to be effective in the treatment of severe toxemia[13]. Administered by either route, an initial dose of 2.5 mg. is recommended, repeating this dose every 8 to 12 hours as needed. Lindley[23] has used larger doses from 5 to 10 mg.; the first dose being given intravenously to speed the onset of action. He found parenteral reserpine effective in 211 of 303 patients, but 89 patients required Apresoline in addition. The onset of action following intravenous administration of reserpine is 60 minutes; the maximum effect occurring in 2 to 4 hours; the duration of action is 6 to 24 hours[33]. Maternal relief of anxiety is a beneficial side effect; although somnolence may occur, the patients can be easily roused.

Side effects most frequently encountered with reserpine are nasal congestion and drowsiness. In view probably of the short duration of therapy, mental depression has not been noted. Because of its delayed onset of action, reserpine should not be used as the sole form of therapy in convulsive eclampsia. In connection with this, parenteral Apresoline may be added either as a single undiluted injection or by intravenous infusion since its onset of action is 10 to 15 minutes. Reserpine added to Apresoline enhances the hypotensive effect of both drugs and prolongs the duration of action; thus it permits the use of smaller doses of the more potent agent and allows for fewer side effects[13]. With the addition of 2.5 mg. reserpine intramuscularly, the intravenous dose of Apresoline may be reduced from 40 mg. to 10 or 20 mg. Inasmuch as reserpine potentiates the sedative effect of barbiturates, the two agents should not be administered concomitantly[34]. Finnerty[13] has warned of the difficulties in anesthetic management that may arise at the time of delivery when reserpine has been employed. Blood pressures may fall to shock levels, particularly after saddle block with procaine[8,13].

Evaluation of the effects of reserpine in the newborn indicates that nasal congestion and increased tracheobronchial secretions may be noted for 24 to 48 hours after delivery, necessitating special pediatric care[5,13]. Rogers[24,31] reported these side effects in 6 of 96 infants. He recommends the use of ¼% Neosynephrine nose drops as needed, with the warning that those infants should not be placed on their backs. The treatment of nasal congestion in the infant has been minor compared with the problem of deep narcosis that occurs with heavy barbiturate and morphine sedation.

Discussion. The records of 1000 maternal deaths and 30,000 stillbirths and neonatal deaths annually from toxemia indicates a need for improvement in the management of toxemia of pregnancy[23]. Primary causes of maternal death have been cerebral vascular accidents, pulmonary edema, and renal failure. Hypotensive drugs may be helpful in relieving vasoconstriction in the affected organs, thus improving blood flow and function. Regardless of the results of depressor therapy, one must use caution in evaluating improvement in the patient's condition. Fetal survival is not necessarily enhanced by good blood pressure responses or symptomatic improvement in the mother. Termination of pregnancy must still be performed at the moment most likely to assure fetal survival and least likely to injure the mother. It should not be forgotten that the incidence of maternal vascular damage following toxemia is proportional to the duration and not to the

severity of the process. The major use of hypotensive drugs appears to be in allowing the pregnancy to continue with safety to the mother and fetus. When the stage of viability of the fetus has been reached, there is no advantage in allowing a toxemic pregnancy to continue if it is not adequately controlled by treatment. Once toxemia develops, fetal growth is slowed. If the toxemic state continues, the incidence of vascular damage to the mother is increased.

The only known cure for toxemia is delivery of the fetus. Although hypotensive drugs help to relieve the generalized vasoconstriction, they do not eliminate the basic etiology. One must adapt the treatment to the individual, depending on such factors as severity of the toxemia, duration of the pregnancy, basic cardiovascular or renal disease, the trend of the blood uric acid and albuminuria, estimated fetal size, and the condition of the cervix, in order to determine when and how to deliver the fetus. In the mildly preeclamptic mother one may try to prolong pregnancy until at least the thirty-fifth week. If symptoms of toxemia still persist then, fetal survival will be enhanced by delivery. Abrupt separation, or infarction of the placenta, is prone to occur if pregnancy is prolonged under these circumstances. The maternal mortality rate for preeclampsia is low; the usual cause of death is progression to eclampsia.

In severe eclampsia, pregnancy should be terminated as soon as it is possible to stabilize the blood pressure, correct pulmonary edema, and control convulsions. This may be accomplished more rapidly with drugs having a specific antihypertensive action than with massive sedation.

Unfortunately, control may not be relaxed even when delivery of the fetus has occurred. Approximately one-fifth of eclamptic patients may have their first convulsion during the 24- to 48-hour period immediately after delivery.

Summary. We have discussed the changing circulatory dynamics during pregnancy in terms of the problems they impose on the patient with essential hypertension or toxemia of pregnancy. Recent views concerning the influence of sodium retaining corticoids on toxemia are presented. The disease process may be listed in ascending order of severity, as follows: (1) Benign essential hypertension, (2) toxemia, (3) essential hypertension with superimposed toxemia, and (4) eclampsia with oliguria, convulsions and coma. The laboratory tests, along with the history and physical examination, that may aid in the differentiation of these various groups are described.

The spectrum of treatment presented is aimed at control of the two major problems in toxemia; the excessive retention of water and salt, and generalized arteriolar spasm with hypertension. It is apparent that the hypertension of toxemia responds poorly to the ganglionic and adrenergic blocking drugs. Among the centrally blocking agents, the use of veratrum alkaloids, Apresoline, and reserpine is discussed. A combination of reserpine and Apresoline constitutes potent therapy. As a single agent, parenteral reserpine is probably the agent of choice for the management of toxemia of late pregnancy.

Finally, the fact must not be lost sight of that delivery of the fetus represents optimum therapy and that the current role of the antihypertensive drugs is in allowing prolongation of gestation safely to the point of fetal viability.

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SEMINAR ON PSYCHOPHARMACOLOGY

Psychopharmacology. CARL F. SCHMIDT, M.D. (Laboratory of Pharmacology, University of Pennsylvania). To medical disciplines other than psychiatry pharmacology has made significant contributions along two lines: a) better therapeutic procedures, by providing means for measuring the effects of existing agents and for evaluating new ones; b) better understanding of the body mechanisms upon which drugs play in producing their characteristic effects. The recent successes of the tranquilizing and hallucinogenic drugs have challenged pharmacology to hazard its laurels in an area that has proved distressingly resistant to the other medical sciences. Many pharmacologists have reacted to this challenge and at a symposium on Psychopharmacology at the XXth International Physiological Congress in August, 1956, some progress was reported. Much of this took the form of discrediting previously attractive hypotheses. Thus, serotonin could be excluded as an essential factor in the actions of tranquilizing and hallucinogenic drugs, because: (a) some hallucinants do not antagonize serotonin (adrenochrome, mescaline, cannabinol, nalorphine, WIN 2299, ethionine), (b) some serotonin antagonists do not cause hallucinations (bromo LSD, ergotamine, ergonovine, medmain), (c) serotonin liberation is associated with the tranquilizing effect of reserpine but not that of chlorpromazine, and (d) the noradrenaline content of nerve tissue varies consensually and concomitantly with the serotonin level. The latter finding suggests that fluctuations in serotonin level may be results rather than causes of altered neuronal activity. Similarly the indole nucleus, found in a number of potent hallucinogens (adrenochrome, bufotenin, yohimbine, LSD), is lacking in many others (cannabinol, mescaline, nalorphine, ethionine, hydralazine, cortisone, dibenamine, cholinesterase inhibitors). Such findings suggest that similar effects from different chemical molecules are probably referable to a peculiarity of the tissues involved.

Along the latter lines, inhibitory neurons in the reticular formation of the midbrain appear to be prominently involved in these drug actions. The tranquilizers increase the activity of these neurons, probably by blocking impulses from functionally opposed sympathetic centers. Higher centers are also involved because blocks produced by tranquilizers in the midbrain and spinal regions are removed by transection of the brain stem and spinal cord respectively. The hallucinogens presumably act on the same structures in the reverse direction. The location is one in which central analgesics and antipyretics produce their effects and from which autonomic influences originate. The relationships between these neurons and mental functions are a promising field for investigation.

Correlation of Some Pharmacological Actions of Phenothiazines in Ani-

mals With "Ataractic" Action in Humans. J. SEIFTER, M.D., A. J. BEGANY, A.B., J. M. GLASSMAN, PH.D., M. HOSKO, M.A., H. PLESS, M.S., E. GORE, M.S., AND R. TISLOW, M.D. (Wyeth Institute for Medical Research). A series of phenothiazines was investigated pharmacologically and an attempt was made to correlate their actions with ability to control psychomotor discharge in patients. In these, either C–C–NR_2, or –C–C–NR_2 chains were substituted on the nitrogen at position 10 of the phenothiazine nucleus. Some of the compounds had a branched methyl group on one of the carbon atoms of the chain. In addition, chlorine or ketone groups were substituted at the 2 position of the phenothiazine ring. The series contained several isomeric pairs. The actions studied were: 1) acute toxicity, 2) antihistaminic, 3) adrenolytic, 4) curariform, 5) antiemetic, 6) potentiation with barbiturates, 7) effect on electroencephalogram, 8) behavioral changes in untreated monkeys, 9) suppression of audiogenic seizures in rats, 10) control of morphine mania in cats, 11) control of psychomotor discharge in acutely agitated patients. The studies in monkeys were useful in predicting the degree of depression obtained in patients but did not always select the clinically useful compounds. The closest correlation between clinical activity and pharmacologic action was obtained in morphinized cats. The clinically active compounds had an intact phenothiazine nucleus, the nitrogen of which carried a three carbon chain with a terminal dialkyl-amino group. Shortening the chain to two carbon atoms resulted in loss of ataractic activity as exhibited by the isomeric pairs promazine-promethazine and chlorpromazine-chlorpromethazine. Lengthening the chain to four carbon atoms also resulted in loss of activity. Addition of a methyl group to the three carbon chain resulted in a decrease or complete loss of activity. Increasing the number of carbons attached to the terminal nitrogen did not result in loss of activity until the total was six carbon atoms. Conversion of the terminal nitrogen into a pyrrolidyl or piperidyl ring did not result in loss of activity. Substitution by chlorine or acetyl in the 2 position resulted in compounds which were more potent pharmacologically but not more potent clinically.

Some Pharmacological Inter-relationships Between Methylphenidate (Ritalin) and Reserpine. ALBERT J. PLUMMER, M.D., PH.D., ROBERT A. MAXWELL, PH.D., AND ALFRED E. EARL, V.D.M. (Research Department, Ciba Pharmaceutical Products Inc., Summit, N.J.). Methylphenidate (α-phenyl-2-piperidyl methyl acetate hydrochloride) produces psychomotor stimulation in the mouse, dog, cat, rabbit and monkey. The peripheral effects of methylphenidate are not marked and little change in blood pressure accompanies increased motor activity.

The sedated state with decreased spontaneous activity following reserpine in the dog is antagonized by oral or parenteral administration of methylphenidate. Reserpine is longer acting and the quiescent state returns after several hours.

Miosis and the relaxed nictitating membrane following reserpine are antagonized by methylphenidate. Relaxation of the nictitating membrane following ganglionic blockade is not affected by methylphenidate, indicating that the antagonism toward reserpine is located centrally to the sympathetic ganglia.

Decreased spontaneous activity and accompanying ptosis produced in mice by reserpine are counteracted by methylphenidate. Sedation of the mice

as estimated by the length of time that equilibrium can be maintained on a rotating glass rod is antagonized by methylphenidate.

Hypothermia produced in monkeys by reserpine is corrected by methylphenidate. Alterations in behavior and body temperature follow parallel courses.

Chronic administration of reserpine in daily oral doses (30 μg. to 60 μg./kg.) lowers the blood pressure of unanesthetized dogs and decreases the lability of the blood pressure in surgically prepared neurogenic hypertensive dogs. Methylphenidate prevents the attendant drowsy state of these dogs without interfering with the hypotensive action of reserpine.

In summary, methylphenidate counteracts several actions of reserpine which are reflections of decreased central sympathetic tone produced by the latter. The hypotensive effect of reserpine is more resistant to antagonism by methylphenidate than is its sedative action. Since methylphenidate exerts no significant hypertensive influence in the dog, it is suggested that its antagonism against reserpine is not mediated by direct stimulation of central sympathetic centers but rather by activation of other areas of the brain inhibitory to the depressant action of reserpine on sympathetic tone.

The Effect of Chlorpromazine and Meperidine, Separately and Combined, on Respiration in Man. HERBERT WENDEL, M.D. CHRISTIAN J. LAMBERTSEN, M.D., AND JOHN B. LONGENHAGEN, Med. Student (Laboratory of Pharmacology, University of Pennsylvania School of Medicine).* The effect of chlorpromazine on the action of other drugs, frequently called "potentiation," might consist in prolongation or intensification of a drug effect, or both. In the latter case the combined effect of chlorpromazine and another drug might be smaller, equal to, or greater than the sum of the separate effects. Discrimination between the different forms of potentiation is important as regards the possible mechanisms of interaction between chlorpromazine and another drug as well as the practical consequences, particularly when toxic drug effects are potentiated by chlorpromazine.

Investigation of this question requires objective measurement of the separate as well as combined effects of chlorpromazine and the potentiated drug. In contrast to sedation hypnosis, anesthesia, and analgesia, the most important drug actions potentiated by chlorpromazine, effects on respiration, as a centrally controlled function, can be easily and objectively measured in man. Respiratory depression is also the most serious toxic effect of most of the drugs potentiated by chlorpromazine.

Separate and combined effects on respiration of chlorpromazine and meperidine were studied in 6 healthy men. Effects were measured at a controlled "alveolar" pCO_2 of 46 mm. Hg as changes in respiratory minute volume before and at intervals after intramuscular drug injection: 25 and 50 mg./70 kg. chlorpromazine depressed, on the average, respiration insignificantly. The results suggest that depending on individuals the drug may depress or stimulate respiration. Chlorpromazine, 25 mg./70 kg. injected with 100 mg./70 kg. meperidine intensified and prolonged respiratory depression of meperidine. Average intensification over a 3-hour post-injection period was 1.4 times the effect of meperidine alone, and 17% more than the sum of the separate effects of the two drugs. In one subject the combined effect depressed respiration to a hypoxic level. Reduced

*Supported by Smith, Kline & French Laboratories, Philadelphia.

ventilation below the peak meperidine depression lasted for more than 4 to 6 hours longer. Of the conceivable mechanisms which could account for the observed effects of chlorpromazine on meperidine depression of respiration the assumption that chlorpromazine inhibits metabolism of meperidine would best fit the results.

An Evaluation of the Uses of Pharmacological Agents in Human Psychiatric Investigation. By JAMES H. EWING, M.D., AND KARL RICKELS, M.D. (Dept. of Pharmacology, University of Pennsylvania School of Medicine). Psychiatrists investigate psychological phenomena which have biological correlates. Many important psychiatric variables are unknown, uncontrollable, must be inferred or their essential nature is not determined. The psychiatric investigator seeks to correlate data from multiple frames of reference. Fortunately some significant psychological variables can now be quantified.

In psychiatry, drugs are used as tools to produce or alter mental phenomena, and to establish prognostic and diagnostic criteria. Careful selection of patients and of psychological methods is required. A representative survey of the methodological possibilities would include attention to the techniques of consensual clinical validation, hi-fidelity recording and photography, the use of check lists and card sorts. Verbal and nonverbal behavior of individuals and groups can be quantified, as the linguists, for example, have shown. Environmental factors in the patient's past experience and in the experimental situation are studied. Components of the clinical mental status examination, such as auditory digit span and word frequency under distraction are singled out and measured. Techniques for studying, learning and conditioning with or without conscious discrimination are successfully applied in humans as well as in animal subjects. Projective techniques are used to evaluate complex psychological functions, although the interpretation of these tests is subject to bias. The psychology and neurophysiology of perception provide a promising area for obtaining quantitative data. Tests of motor performance and coordination yield data of varying precision.

Psychiatric research is progressing, however slowly, toward the goal of quantifying data. Investigations correlating clinical ratings of free anxiety with psychological tests, various physiological and biochemical measurements, such as blood-glutathione level, hippuric acid excretion and corticosteroids in urine and plasma are illustrative. For example, we have found high correlations between hippuric acid excretion (values corrected for weight, age and urine volume), clinical judgments of free-anxiety by three raters, and ratings on the Taylor Manifest Anxiety Scale.

BOOK REVIEWS AND NOTICES

MODERN OFFICE GYNECOLOGY. By GEORGE BLINICK, M.D., F.A.C.S., and SHERWIN A. KAUFMAN, M.D., F.A.C.S. Pp. 218; 47 ills. Philadelphia: Lea & Febiger, 1957. Price, $4.50.

Too few physicians are familar with the simple tests which they can use in the office to determine the cause of common gynecologic symptoms and the treatments which will relieve them. The authors of "Modern Office Gynecology" have attempted to prepare a text from which the busy practitioner can readily obtain specific information to help him study and treat women with pelvic disorders.

The book is divided into three sections, the first of which deals with various symptoms such as abnormal vaginal bleeding, infertility, vaginal discharge, menopause, and others. Diagnostic procedures are described and treatment methods are outlined. The second section consists of 47 good drawings to illustrate the text material previously presented. The third section, an annotated Bibliography, is a series of abstracts of papers referred to during the initial discussions.

The methods described are those used by the authors and, for the most part, they are acceptable. Occasionally, however, they bow to the weight of authority or tradition and the result is confusing. For instance: "Curettage should be done if bleeding continues for two weeks, sooner if bleeding is profuse. In our opinion the most expeditious treatment of incomplete abortion is by early curettage in order to avoid the uncertain outcome of conservative therapy. . . ."

The book is a bit difficult to read because of its division. One must thumb through the pages many times to find the appropriate illustration and to refer to the summarized references. The latter at least might be more advantageously included with the material in the first portion of the book.

The authors have directed the book toward general practitioners and specialists rather than medical students. The practicing gynecologist should be completely familiar with all the material presented and probably will find little to help him with his problems. It should be more useful to the family doctor, but its value is limited by the fact that the main concern is with symptoms themselves rather than their underlying causes. J. W.

THE VISUAL FIELDS. By DAVID O. HARRINGTON, A.B., M.D., Clinical Professor of Ophthalmology, University of California School of Medicine. Pp. 327; 234 ills. and 9 color plates. St. Louis: C. V. Mosby Co., 1956. Price, $16.00.

PERIMETRY is the clinical investigation of the functional integrity of the second cranial nerve from its recipient end organs in the retina to the perceptual area in the calcarine cortex of the cerebrum. It is one of the most accurate and precise of all methods of clinical examination. To know its techniques, and interpret its findings is a complex and difficult undertaking. This is true because so many different disciplines are involved. Proper perimetry presupposes proficiency in optics, in anatomy of the eye and brain, in physiology of the visual apparatus and the central nervous system, as well as a comprehensive knowledge of ocular and cerebral disease. Confronted with these complexities, many ophthalmologists unfortunately relegate this all-important study to underlings.

Harrington has taken this complex subject and simplified it by the use of excellent comprehensive illustrations, combined with a very readable and easily understood narrative. He presents the necessary basic material in proper perspective. He has cleared many of the perplexities in technique. He presents the interpretation of field defect with unusual success. He has caught, and portrayed the beauty, the importance, and the informative nature of perimetry.

No neurologist, neurosurgeon, or ophthalmologist should be caught without a copy of this book in his library. G. G.

DISEASES OF THE HEART AND CIRCULATION. By PAUL WOOD, M.D., Director, Institute of Cardiology, London; Physician, National Heart Hospital. 2nd ed. Pp. 1005; 473 ills. Philadelphia: J. B. Lippincott Co., 1956. Price, $15.00.

THIS book deserves careful critical reading. The author is obviously a forceful person, occupying a commanding position in the hierarchy of British cardiology, and so exerts strong influence on English-reading cardiologists. There is an overemphasis on disorders amenable to surgery. Thus, the section on congenital heart disease is three times as

long as that on coronary artery disease. The simple, direct and pleasing style makes for easy reading.

But this style is partly due to dogmatism and to ignoring evidence which displeases him. To cite but a few examples: digitalis intoxication (p. 731), permanent aggravating effect of pregnancy on mitral stenosis (p. 546), abortion for thyrotoxicosis (p. 909), the enlarged left atrial of mitral stenosis a result of atrial fibrillation (p. 526), Broadbent's sign (p. 58), the relationship of symptoms to pulmonary vascular resistance in mitral stenosis with atrial fibrillation, the ancient reference (p. 786) that hypertensive persons with negative T-waves in left ventricle surface leads die within 8 months, Truetta's work (p. 766), that professional men have a higher incidence of coronary artery disease. The illustration for the exercise test is poorly chosen because the resting electrocardiogram is obviously abnormal.

The author extracts more information from clinical observation of the jugular venous pulse and from palpation of the brachial artery than anyone known to the reviewer. But when he observes radiologically that the left ventricle in mitral stenosis is hypodynamic and fills slowly (p. 532), his observation appears to the reviewer an hallucination produced by logic. The same may be said for the straight line curve obtained by measuring on conventional films an imaginary pulmonary artery. The author universally mistakes the left auricle and pulmonary artery for the atrium.

Yet this book should be read carefully and critically by all cardiologists because it is written in the old manner of a great clinical text. Except possibly for the sections on hypertension and coronary artery disease, the author paints a vivid picture of his convictions based upon a distillation of his own obviously tremendous personal experience. There is nothing in this book which suggests a hermit sitting in the library with a large pair of scissors. L. S.

PERSONALITY, STRESS AND TUBERCULOSIS. Edited by PHINEAS J. SPARER, M.D., Professor of Psychiatry and Preventive Medicine, University of Tennessee College of Medicine. Pp. 629; 14 ills., 30 charts. New York: International Universities Press, Inc., 1956. Price, $12.50.

THAT there is some relationship between personality, life-situation, and clinical tuberculosis has long been recognized by observant and experienced clinicians. In recent years two concepts have given great impetus to studies of these complex relationships. Psychosomatic medicine emphasizes "what kind of patient has a disease." The General Adaptation Syndrome of Selye has turned the spotlight of research upon hormonal mediators in the stress reactions. Titration of these hormones is possible, though often only by roundabout methods. Unfortunately, titrations of personality are even more roundabout, less precise, and more likely to be weighted by the personal views of the reporter. It was inevitable that under the double stimulus of the psychosomatic concept and the General Adaptation Syndrome a new attack would be made upon the age-old problems of human tuberculosis.

This volume is a collection of 33 papers by recognized authorities, originally presented for the psychosomatic orientation of the staff of the Memphis Veterans Administration Hospital. The high quality of the contributions wisely led to their publication under the able editorship of Dr. Sparer. There is, naturally, a certain amount of duplication as well as some contradiction. On the whole, the material is fresh, well presented, and very stimulating. Format is pleasant, Index is included, bibliographies are extensive.

In the United States, and in many other countries of approximately equal social and economic status, the tuberculosis problem is undergoing rapid and profound change. No longer epidemic, the disease is still stubbornly endemic. More is required than public health measures (isolation) and treatment aimed solely at suppressing bacilli or excising diseased tissue. The relapsing patient, the recalcitrant patient, and the newly infected patient will all benefit from the sound application of the "holistic" approach set forth in this excellent book. R. C.

ALLERGIC DERMATOSES. Edited by RUDOLF L. BAER, M.D., New York University Postgraduate Medical School. Pp. 110; 2 ills. Philadelphia and Montreal: J. B. Lippincott Co., 1956. Price, $3.00.

THIS little volume is one of the practitioners' pocket books which Lippincott has put out on a variety of subjects. It deals with a restricted phase of allergy (allergic dermatoses due to physical agents). The subject matter is discussed by a number of experts in the field and includes: (1) Hypersensitivity to Trauma; (2) Eczematous and Polymorphous Hypersensitvity to Light; (3) Urticarial Hypersensitivity to Light; (4)

Hypersensitivity to Heat; (5) Cutaneous Sensitivity to Cold. The illustrations are good and the Index and Bibliography are more than adequate. In spite of the fact that the various chapters were prepared by different individuals, the style is fairly uniform throughout. The material is discussed on a high plane and the tendency is to emphasize what is not known as well as what is known about physical allergy. The book is an authoritative and convenient source on this subject. H. B.

SURGERY IN WORLD WAR II. VOLUME II. GENERAL SURGERY. Editor-in-Chief: COLONEL JOHN BOYD COATES, JR., MC; Editor for General Surgery: MICHAEL E. DEBAKEY, M.D.; Associate Editors: W. PHILIP GIDDINGS, M.D. AND ELIZABETH M. MCFETRIDGE, M.A. Pp. 417; 45 ills. Washington, D.C.: Office of the Surgeon General, Department of the Army, 1955. Price, $4.25.

THIS volume presents the experiences with abdominal injuries in the Army during World War II. Multiple authors have contributed and the sections are well arranged with an interspersing of excellent illustrations. Part One deals with resuscitation and anesthesia; Part Two with abdominal wounds and their initial surgical treatment; and Part Three discusses colostomy. It is only during a war that such great experience with severe trauma is obtained and these lessons should be utilized by all surgeons. Some of the outstanding advances in knowledge are represented by the importance of adequate and prompt volume replacement for wound shock and the feasibility and importance of prompt surgery and adequate debridement. The attack on thoraco-abdominal wounds and drainage for liver injuries are discussed in detail. Another fact presented is that colostomy is the prime modality in all wounds of the colon and that intraperitoneal closures are usually the most advisable.

This volume should be read by all surgeons engaged in the treatment of trauma and should be used as a guide in planning for the surgery of mass casualties. R. B.

RHEUMATOID ARTHRITIS AND PSORIASIS VULGARIS. By TIBOR BENEDEK, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Stritch School of Medicine, Loyola University. Pp. 308; 57 ills. Privately published. Distributor: Chicago Medical Book Company, Chicago 12, 1955. Price, $12.00.

FOR purposes of review, this monograph is best described under separate headings devoted to 1) comprehensive surveys of literature relating to the pathogenesis and treatment of arthritis and psoriasis, and 2) a running account of the author's 30 years of research which have led him to a new and extraordinary hypothesis as to their etiology.

The chapters which review older ideas of etiology deserve high praise. They deal effectively with the minutiae and yet throw these into perspective so that the field can be quickly and authoritatively surveyed from the point of view of current thinking without, however, losing sight of the older literature, much of which is in danger of being forgotten.

However, the main purpose of the book is to defend the author's hypothesis that the "*Bacillus endoparasiticus* Benedek 1927" is the fundamental cause of the following diseases: psoriasis vulgaris, pomphylox, pityriasis rosea, hydradenitis suppurativa, sporiatic arthritis, peripheral and spondylitic rheumatoid arthritis. The organism is believed to be a permanent endoparasite causing the lesions of the above diseases by bacterial allergy in response to varying degrees of bacteremia. Because this claim, particularly in the case of rheumatoid arthritis, re-introduces the long-discarded theory of bacterial causation, it is apt to be rejected without even being adequately studied. Therefore, in order that Dr. Benedek may get a fair hearing, his hypothesis must be presented in more detail than is customary in a review of this kind.

Benedek's Bacillus, as the author points out, had been previously described in connection with studies on rheumatoid arthritis by Schuller in 1892, by Bannatyne in 1898 and by Fayerweather in 1905. It is questionably distinguishable from the common bacterial contaminants *B. subtilis*, *B. cereus* and *B. megatherium*. Human cultures are best obtained from cantharides blisters or from the buffy coat of a centrifuged specimen of citrated blood. Not infrequently it can be identified in histological preparations, but only when stained with Weigert's lithium carmine Gram stain.

In the case of rheumatoid arthritis, positive blood cultures were obtained in 105 consecutive patients. However, this startling finding is offset by the even more astounding claim that the bacillus can be routinely cultured in over 90% of normal, healthy human beings irrespective of race. Dr. Benedek also claims to have isolated it from arterial and venous blood in 31.7% of 657 umbilical cords. Thus, Dr. Benedek is driven to onclude that

the whole human race is permanently infected by his organism which is transmitted routinely from the mother to the fetus during gestation. This "endoparasitism" is permanent since, although the organism is susceptible to several antibiotics, it is a spore former and so cannot be eradicated. As long as the organism and host are in "equilibrium," health is not affected, but when this equilibrium is disturbed by "factor X" the above mentioned diseases are precipitated.

It seems to this reviewer that, even if Dr. Benedek's hypothesis of permanent endoparasitism be granted, it would be exceedingly difficult to prove that it has anything to do with the etiology of the diseases under consideration. As Dr. Benedek admits, Koch's postulates cannot be fulfilled by his observations. Hence, the proof must be indirect. Perhaps the strongest link in what seems a rather inconclusive series of arguments is the claim that microdosage vaccine therapy is effective in several of the skin diseases mentioned as well as in rheumatoid arthritis. Dr. Benedek claims that 21 of a series of 94 cases of rheumatoid arthritis were "arrested," that is, showed no signs or symptoms of the disease following vaccine therapy with his bacillus. If verified, this would be a highly important contribution to the management of rheumatoid arthritis. The claim, however, must be evaluated in the light of a host of similar claims for various "specific" vaccines which were made long ago, before modern methods of evaluating rheumatoid arthritis were available, and which have long since been discredited.

Although it seems impossible that an organism such as Dr. Benedek describes, which appears to be by no means fastidious, could have been overlooked in the many thousands of blood cultures made on patients with rheumatoid arthritis over the last 50 years, nevertheless, one more effort by a competent bacteriologist who is willing to repeat Dr. Benedek's techniques in detail, would seem justified. One critical study would tell us whether Dr. Benedek's findings, and, therefore, his whole theory, are, or are not, due to contamination by the ever present group of *B. subtilis* type of organisms. J. L.

Roentgen Signs in Clinical Diagnosis. By Isadore Meschan, M.A., M.D., Professor and Director of the Department of Radiology at the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina. Pp. 1058; 2216 ills. Philadelphia and London: W. B. Saunders Company, 1956. Price, $20.00.

This work is organized to serve as a text for the teaching of diagnostic radiology to medical students and as introductory material for postgraduate instruction of residents training in the speciality of radiology. It is systematic in approach and admirably suited to the author's intent. It provides an excellent introduction and guide for the general physician. Its scope is so comprehensive that the treatment of any specific subject is necessarily somewhat dogmatic and incomplete.

There is an excellent chapter on the technical background of radiography and fluoroscopy. It is surprising to find, in a volume so up-to-date and so replete with reliable technical data, the common error repeated of referring to the process of dark-adaptation as "accommodation." The vital and timely subject of patient and physician protection against radiation hazards is well presented.

Bone and lung lesions are classified according to gross radiologic appearances. This is a fresh approach and should prove useful to the general physician or specialist outside radiology using this book as a guide to diagnostic possibilities, as well as in teaching.

H. S.

Ageing in Transient Tissues. Volume 2, Ciba Foundation Colloquia on Ageing. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Elaine C. P. Millar, A.H.W.C., A.R.I.C. Pp. 263; 96 ills. Boston: Little, Brown and Company, 1956. Price, $6.75.

"Ageing in Transient Tissues" is a series of papers which were presented and discussed by a panel of 27 scientists at the second Ciba Colloquium on Ageing. The broad scope of the conference is indicated by the variety of the material contained in the 17 papers: as examples "Organ Culture Studies of Foetal Rat Reproductive Tracts," "The Regenerative Capacity of Ovarian Tissue," "Biochemical Evidence of Ageing in the Placenta," "The Growth Cycle of Deer Antlers," The Metabolism of Senescent Leaves," and "Ageing in Human Red Cells." So much and such varied material was presented that it is impossible to review it in general terms, but it all concerned some aspect of cellular ageing.

The final group discussion, during which the panel members attempted to interpret and correlate the material presented and to define general terms, indicates how difficult it

is to arrive at a single precise meaning for the term "ageing" as compared with "senescence," "differentiation," "maturation," and others. No definite decisions were reached.

The material presented in this volume has far more to interest anatomists, chemists, physiologists, zoologists and other scientists who are working in the field of growth and development than clinicians in any field of medicine. J. W.

PRACTICAL PEDIATRIC DERMATOLOGY. By MORRIS LEIDER, M.D., Associate Professor of Dermatology and Syphilology, New York University Post-Graduate Medical School. Pp. 433; 293 ills. St. Louis: The C. V. Mosby Co., 1956. Price, $10.50.

MORRIS LEIDER's book is in keeping with the trend of the times in that it presents the various aspects of pediatric dermatology in a separate monograph rather than as part of a general dermatologic text. This is not the first presentation on pediatric dermatology but it is one of the most comprehensive. The material is discussed, where possible from the etiological standpoint, in fourteen chapters. It also contains a dermatological Glossary and an Index. The volume is profusely illustrated and there is an abundance of well conceived and executed tables for ready reference and correlation of data. Another feature is a blue section, conveniently placed, which contains 101 dermatologic preparations for topical application. While the balance is in favor of the merits of this book, there are certain shortcomings. The Index is not as detailed as might be desired, or perhaps certain subjects are intentionally omitted (multiple benign cystic epithelioma; histiocytoma cutis; Letterer-Siwe syndrome; eosinophilic granuloma, for example). Dr. Leider is a student of semantics and has a facility of language that is well known to his colleagues. In a way, this has led to distracting and at times tautologic writing. In spite of this, pediatricians, general practitioners and indeed dermatologists have a lot to gain from the compilation. H. B.

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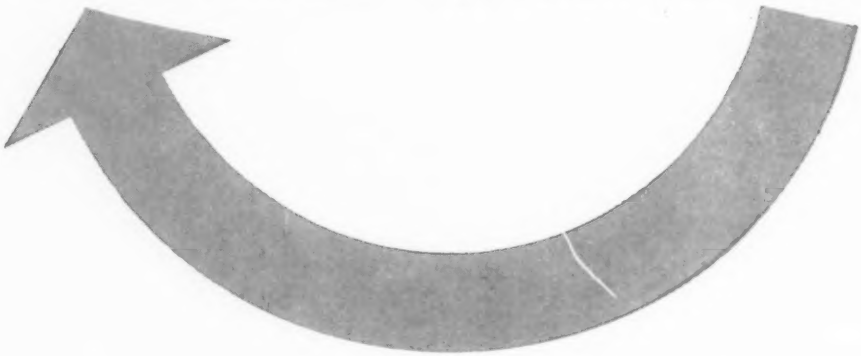

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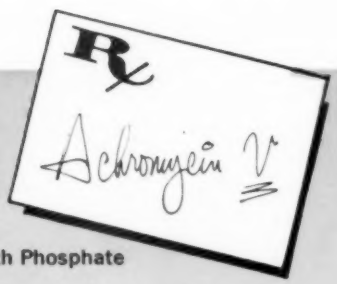

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CAPSULES—Each capsule (pink) contains tetracycline equivalent to 250 mg. of tetracycline HCl, phosphate-buffered. Bottles of 16 and 100 capsules.

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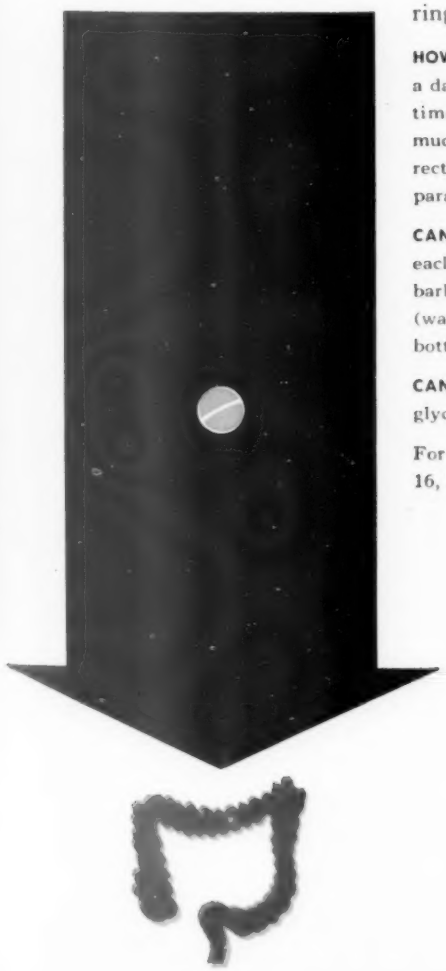

HOW CANTIL IS PRESCRIBED One or two tablets three times a day preferably with meals, and one or two tablets at bedtime for patients with ulcerative colitis, irritable colon, mucous colitis, spastic colitis, diverticulitis, diverticulosis, rectospasm, diarrhea following G.I. surgery, bacillary and parasitic disorders.

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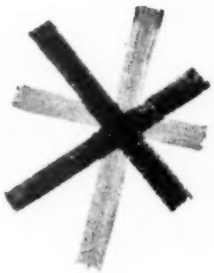

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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955.

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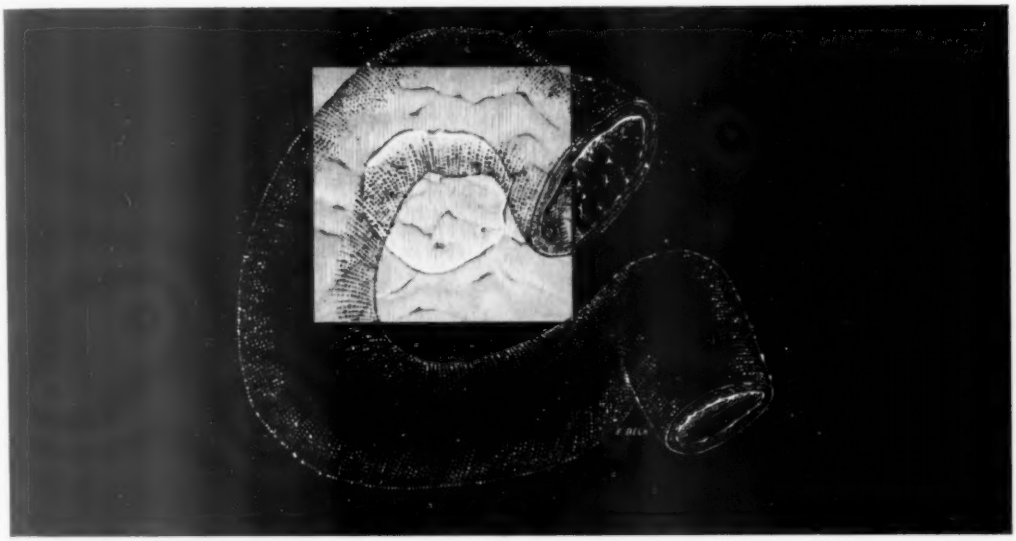

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---

1. Lichstein, J.; Morehouse, M. G., and Osmon, K. L.: Am. J. M. Sc. *232*:156 (Aug.) 1956.

2. Sun, D. C. H., and Shay, H.: Arch. Int. Med. *97*:442 (April) 1956.

3. Rafsky, H. A.; Fein, H. D.; Breslaw, L., and Rafsky, J. C.: Gastroenterology *27*:21 (July) 1954.

4. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

5. Silver, H. M.; Pucci, H., and Almy, T. P.: New England J. Med. *252*:520 (March 31) 1955.

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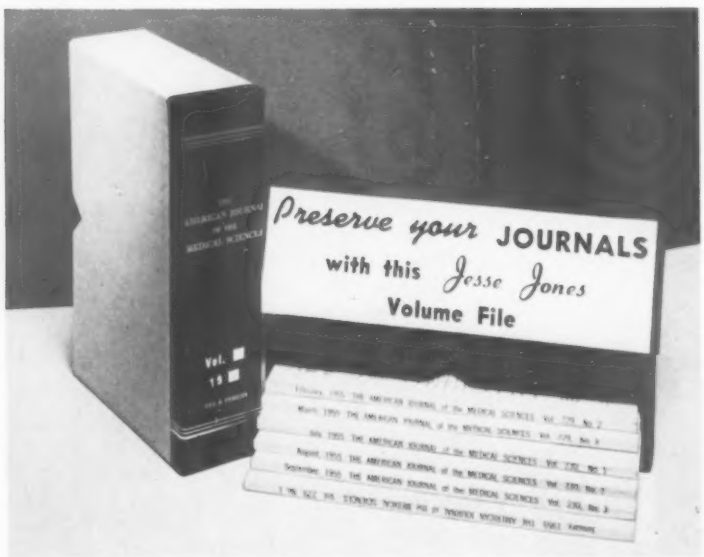

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2

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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat. *5*:778 (Oct. 1954).
2. Freed, S.C.: G.P. *7*:63 (1953).
3. Sherman, R.J.: Medical Times, *82*:107 (Feb. 1954).

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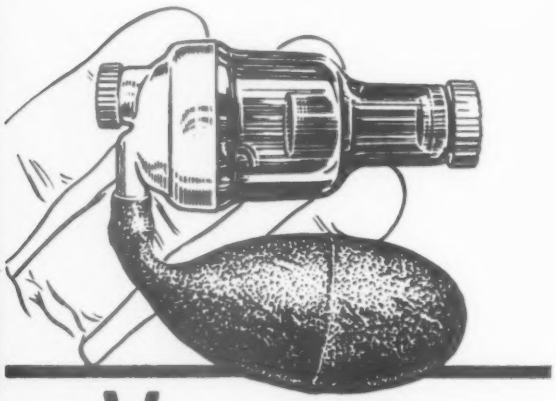

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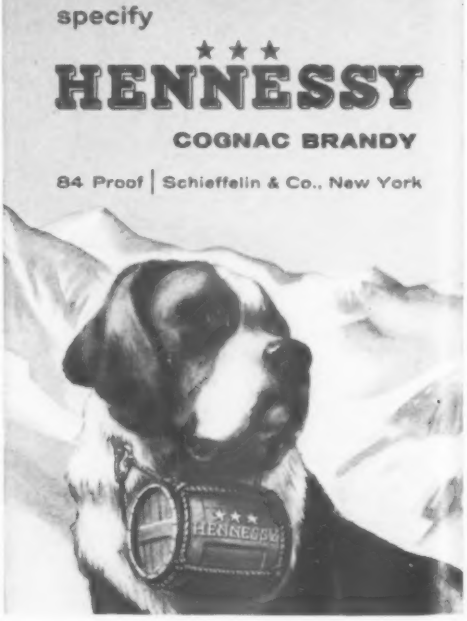

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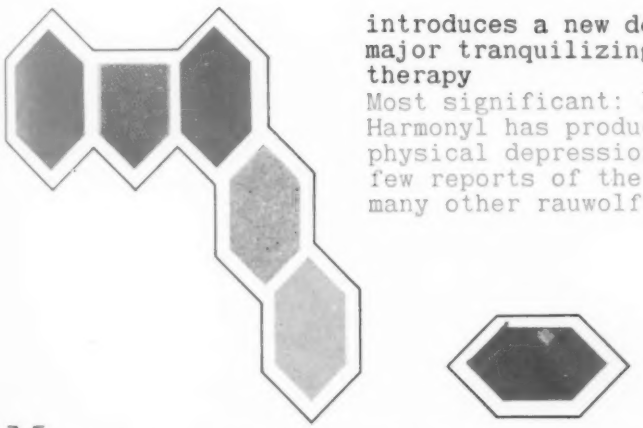

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Following another eight-month study of chronic, hospitalized mental patients, Ferguson[2] stated:

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- Patients experiencing side reactions on reserpine often were completely relieved when changed to Harmonyl.

Ferguson concluded: "*The most notable impressions were the absence of side effects and relatively rapid onset of action with Harmonyl.*"

Comparative studies have shown Harmonyl and reserpine about equal in hypotensive effect. The tranquilizing action of the two drugs also appeared similar—except that few cases of giddiness, vertigo, sense of detached existence or disturbed sleep were seen with Harmonyl.

Professional literature is available upon request. Harmonyl is supplied in 0.1-mg., 0.25-mg., and 1-mg. tablets. Abbott

References: 1. Communication to Abbott Laboratories, 1956. 2. Ferguson, J. T.: Comparison of Reserpine and Harmonyl in Psychiatric Patients: A Preliminary Report, Journal Lancet, 76:389, December, 1956. *Trademark

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*Fiskio, P. W.: GP *11*:70 (May) 1955.

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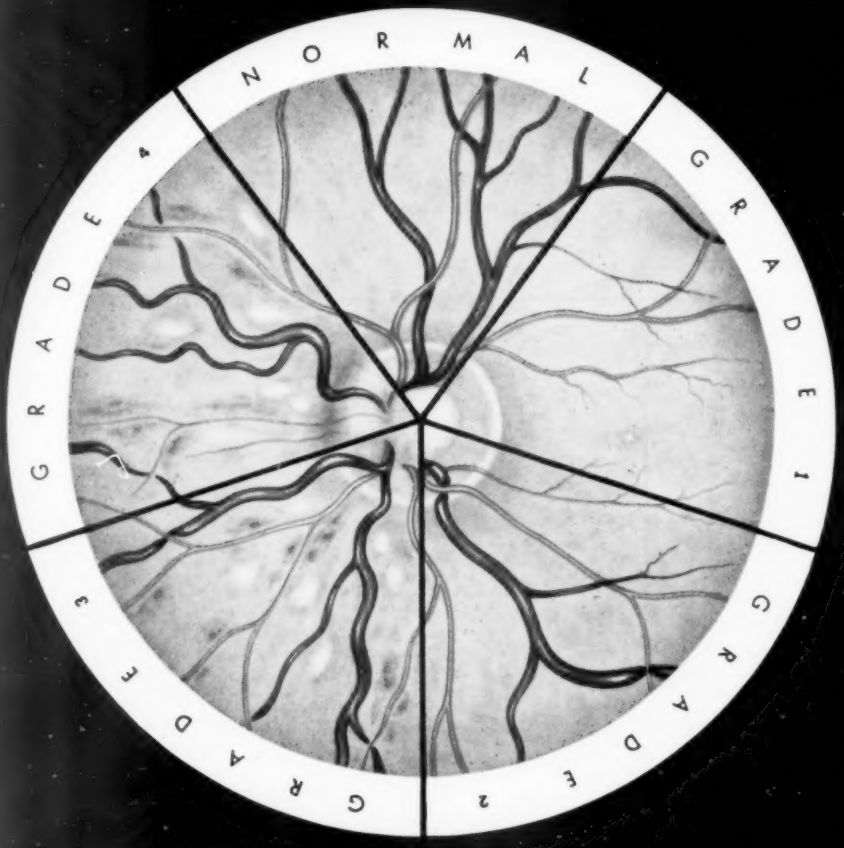

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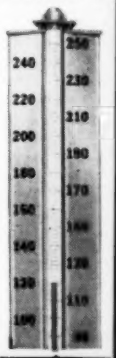

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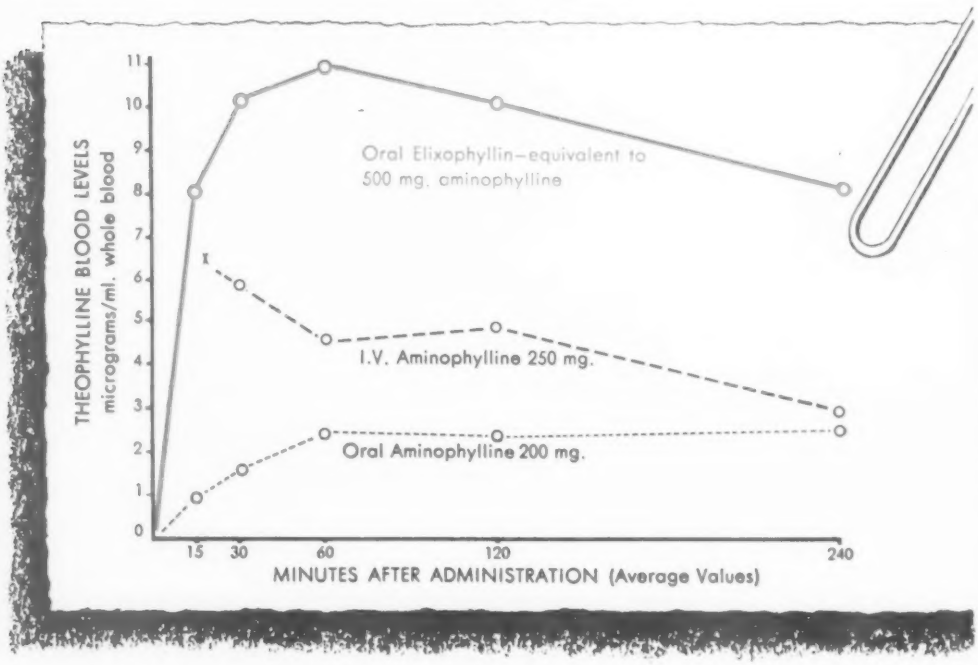

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Elixophyllin data—Schluger, J., et al.: Am. J. M. Sci. 233:296, 1957;
other data—Waxler, S. H. & Shack, J. A.: J.A.M.A. 143:736, 1950.

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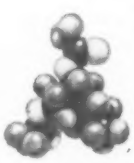

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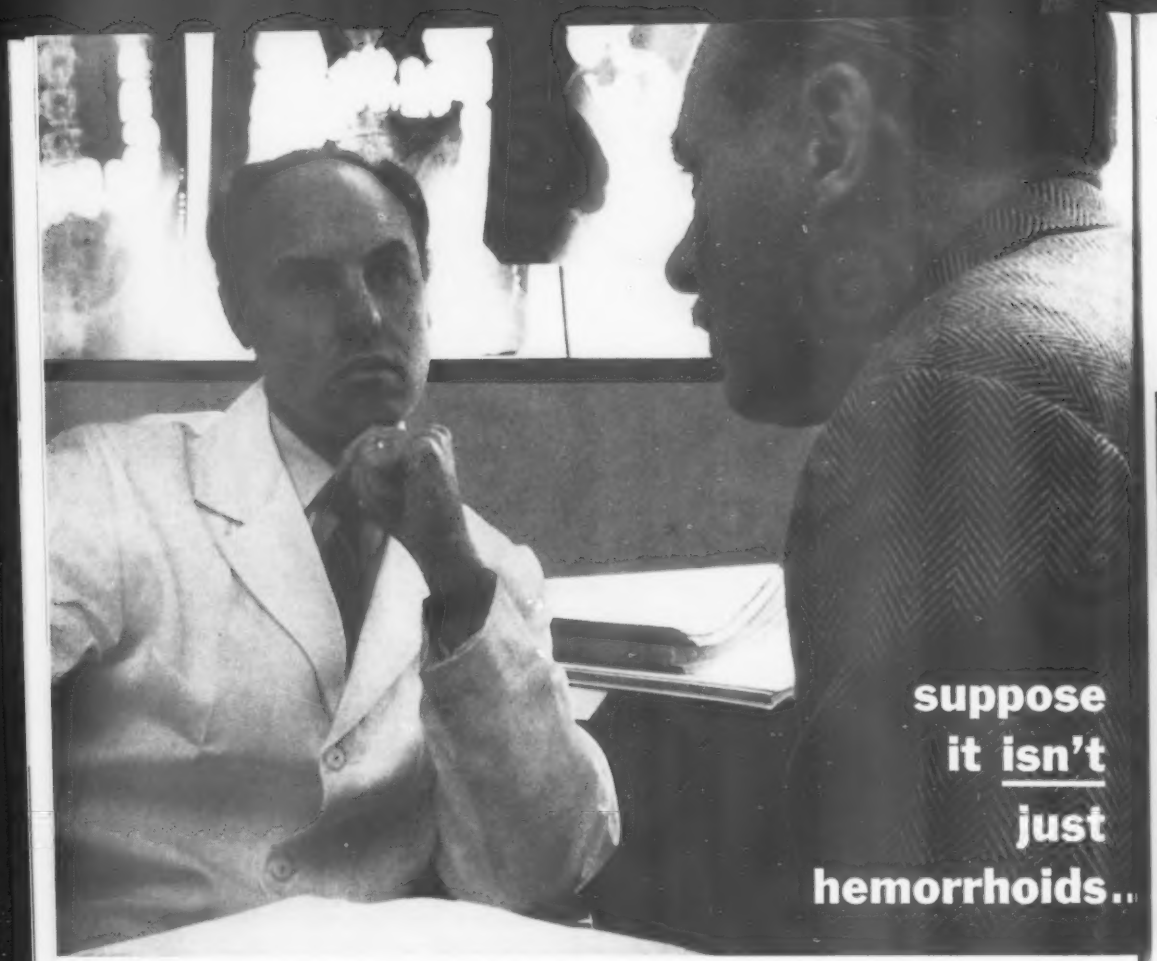

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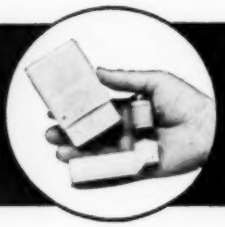

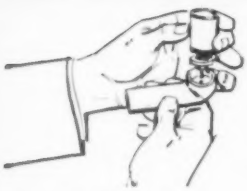

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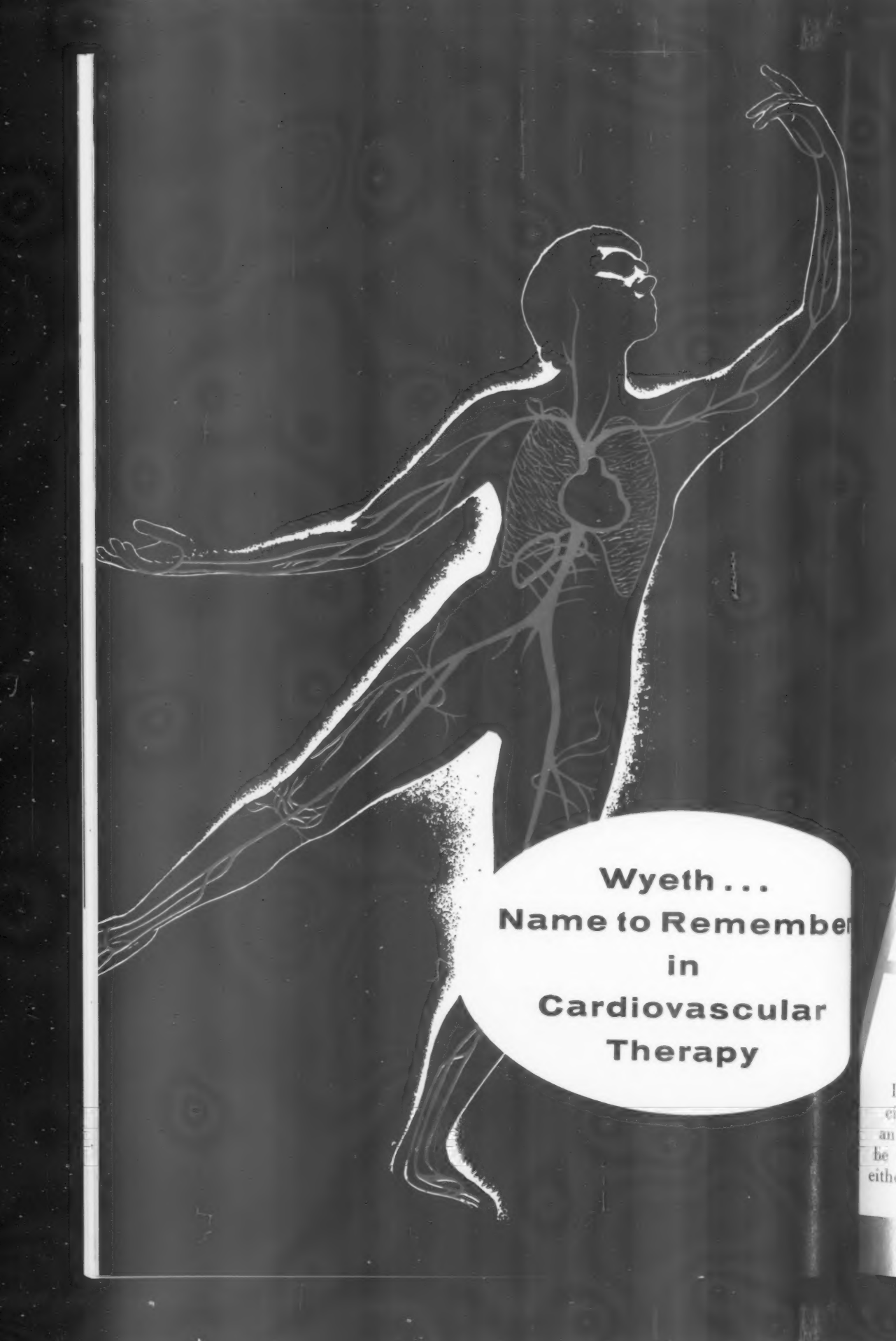
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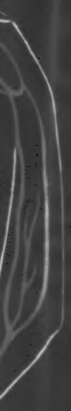

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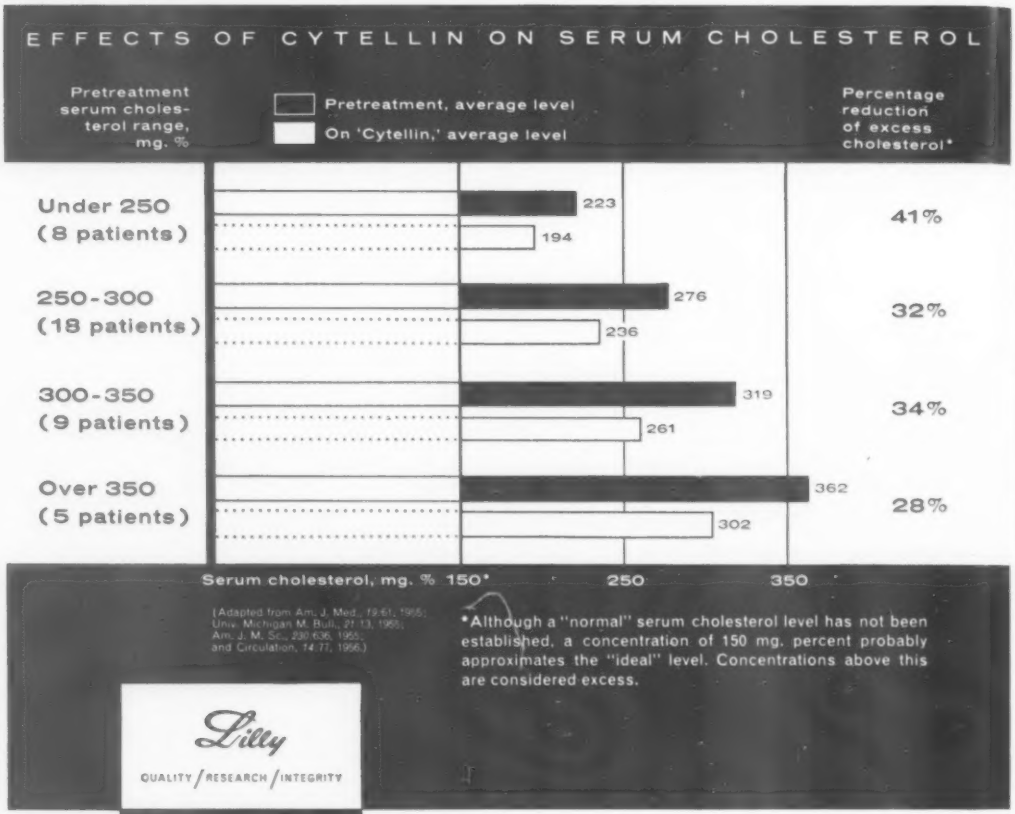
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194
41%
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276
236
32%
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319
261
34%
Over 350 (5 patients)
362
302
28%
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Kessler, L. N. and Barnard, R. D.: M. Times 84:451, April 1956.

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when blood pressure must come down

increased antihypertensive benefits

Lowering of diastolic and systolic pressures
Beneficial bradycardia
Increase in renal blood flow

low dosage of Apresoline

Combined with Serpasil, Apresoline is effective at an average daily dose of only 200 mg. Thus, side effects such as headache and tachycardia seldom occur.

versatility

Easier management of hypertension is made possible by two tablet strengths of Serpasil-Apresoline.

All patients to be given Serpasil-Apresoline may benefit from priming with Serpasil.

SERPASIL-APRESOLINE *Tablets #2* (standard-strength, scored), each containing 0.2 mg. of Serpasil and 50 mg. of Apresoline hydrochloride; *Tablets #1* (half-strength, scored), each containing 0.1 mg. of Serpasil and 25 mg. of Apresoline hydrochloride.

Serpasil®-Apresoline®

hydrochloride

(reserpine and hydralazine hydrochloride CIBA)

COMBINATION TABLETS

CIBA
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invitation to asthma?

not necessarily...

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

relief in minutes...Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours...Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

Tedral provides:

Theophylline	2 gr.
Ephedrine HCl	3/8 gr.
Phenobarbital	1/8 gr.

in boxes of 24, 120 and 1000 tablets

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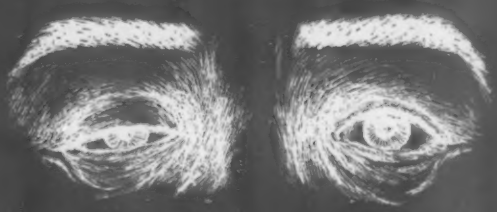

A GREAT STEP FORWARD

in the management of

MYASTHENIA GRAVIS

MYTELASE *chloride*

Brand of ambenonium chloride

(formerly Mysuran chloride)

Mytelase chloride (WIN 8077) is a new antimyasthenic compound with definite advantages over older cholinergics.

More pronounced improvement

Patients "... feel better, are stronger, and are closer to their normal health."[1]

More prolonged action

As a rule Mytelase "... has roughly twice the effectiveness per milligram of neostigmine in reducing the symptoms of myasthenia gravis, and approximately twice the duration."[2] Some patients can replace their former 10 to 60 tablets daily with as few as 2 tablets of Mytelase; sleep need not be interrupted for dosage.[1]

Fewer gastro-intestinal side effects

Supplied: Tablets, scored, of 10 mg. and 25 mg., bottles of 100.

Write for booklet discussing in detail clinical experience, dosage, side effects and precautions to be observed.

1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

Mytelase, trademark

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